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LECTURES

ON

GENERAL PATHOLOGY.

A HANDBOOK FOR PRACTITIONERS AND STUDENTS.

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THE PATHOLOGY OF NUTRITION.

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SECTION II.

THE PATHOLOGY OF NUTRITION.

Introductory remarks on normal tissue-metabolism and its conditions. Trophic nerves.

We placed the Pathology of the Circulation at the head of our discussions, because it occupies in a sense a central position among the whole of the processes taking place in the machinery of the human organism. But before we now turn to the special chapters on digestion, respiration, &c., it appears necessary to take a thorough survey of *the alterations in the constitution of the apparatus* which are actively employed in the organism. For while the circulation affords, it is true, the material for all the activities of the organism and of its individual parts, the manifestation of these activities in this or that determinate form depends on the constitution of the individual apparatus. These must be in order, for life and its physiological functions to proceed regularly; hence every change of constitution, if any way considerable, must be attended by a disturbance of their function. From this, however, it follows conversely that in the pathology of the latter we are continually warned to make ourselves familiar with the conditions, under the influence of which the various organs experience alterations of their chemical and morphological characters.

How completely justified we were in placing the Pathology of the Circulation first becomes evident on considering that it is essentially the circulation which determines the normal constitution of the individual apparatus and organs. For the animal organism and its apparatus do not, as is well known,

act like a machine, which while it works remains itself unchanged and merely transforms the free energy supplied it from without into other kinds of force. Rather the whole of the work done by all the apparatus of the body, and so by the body itself, depends *on chemical processes* taking place within it, by means of which latent is converted into free energy. To the sum-total of these chemical processes the term *metabolism* is applied; and we speak of a metabolism of the organism as a whole, as well as of a metabolism of its individual parts. Just as the whole organism is maintained in a normal state by the general metabolism, so each individual part is preserved by its own metabolism; and every disturbance of the latter must alter the constitution of the apparatus. If, then, we wish, before discussing the pathology of the special functions, to get an idea of the conditions under which the individual apparatus maintain or lose their normal constitution, this involves nothing more or less than *a discussion of their metabolism.* But we can go a step further. For it can scarcely be disputed by anyone at present that the processes by which the nutrition of the organs and tissues is effected take place in the *elementary parts* of these organs and tissues. These, however, are *cells*; or at least *cell-derivatives,* like the muscle- and nerve-fibres, like the fibres and intercellular substance of connective tissue; and thus it is precisely in this portion of pathology that the *cellular theory* assumes its full importance. As a matter of fact the most open opponents of the *cellular pathology* unreservedly recognise its utility as far as the analysis of pathological nutritive processes goes; and according to what has just been said a scientific pathology of tissue-nutrition can only be undertaken on the basis of the cellular theory.

If only the foundation were a better one,—one on which we could go on building! But on looking at the knowledge accumulated by this department of physiology we find that the metabolism of the body as a whole is dealt with in a number of very excellent researches, by which the total income and expenditure of the animal organism, under a great number of varying conditions, have been placed on a secure basis. With the results of these investigations, which in many instances, *e. g.* the metabolism of inanition, touch

upon the domain of pathology, you have been made acquainted in your physiological studies; and you will the more readily dispense with a repetition of them here, as they are elaborately treated of in all the text-books of physiology. But on turning to *the metabolism of the tissues,* we discover that what is known of the exchange of material under normal conditions in the elements of the individual organs is so scanty that this without doubt highly important chapter of general physiology is dismissed with a word or two by the text-books, while in histological treatises it is of course not even touched upon. Our imperfect knowledge of these processes is limited at best to their *commencement* and *termination; i. e.* we are in a position to judge what material is supplied and presented to the tissues and their cells; and are also acquainted, though far from perfectly, with that which, as distinguished from the *income* of the tissues, may properly be called their *expenditure.* To the tissues is conveyed by the lymph or transudation a watery solution, partly perfect and partly imperfect, of inorganic and organic substances, while at the same time oxygen passes over to them from the capillaries. The tissues having obtained their income from these sources, their expenditure occurs in a twofold manner. In the first place they give up carbonic acid and certain organic and inorganic substances to the blood, or to the lymph bathing them which returns the material to the blood. In the second place, a number of organs also dispose of constituents in another direction. Some of these are directly removed from the body, like the horny cells of the epidermis and the most superficial cell-layer of the stratified epithelia, the sebum and sweat, like milk and the mucus of various mucous membranes. Or they are first contained in special preformed channels and receptacles, like all glandular secretions in the interior of the body; and then either finally expelled, as the urine, semen, those portions of the bile and intestinal secretion passed with the fæces; or, in so far as they are resorbed, restored to the juices of the body, like the saliva, gastric juice, &c.

But the processes intermediate between the income and expenditure of the organs and tissues are, in by far the greater part, completely unknown to us. True, that the

water which passes over into the saliva, the urine, &c., is almost altogether the same water which is conveyed by the blood to the organs, and in them simply transudes, does not admit of reasonable doubt. But even the case of the inorganic constituents, the salts, is far from being so simple; while the fate attending the organic substances from the moment of their being taken up by the tissues till the specific constituents leave the organ is almost everywhere involved in deep obscurity. In the first place, we are far from knowing the manner in which the elements of the various organs take up the materials presented to them by the lymph. We do not even know whether from the first they absorb only certain substances, and so go to work on a selected portion, or whether they absorb indiscriminately and afterwards eject what they have failed to assimilate. And we have been obliged to remain in ignorance through failing to discover whether the transudation of all parts, immediately after it has left the capillaries, is identical in constitution, or whether it does not rather present quantitative and even qualitative differences—in favour of which latter view I have adduced many facts. But a still greater impediment to the understanding of these processes is found in the circumstance that we are absolutely unacquainted with the *modus* in which the materials supplied are absorbed by the tissue-elements. Hoppe* has repeatedly pointed out that the assumption of a supply of materials to the elements by diffusion is, for the carbohydrates, at least improbable; and quite untenable for albuminoids, fats, lecithin, &c., inasmuch as these bodies are incapable of diffusion in aqueous solutions. The absorption of the material presented by the lymph must therefore take place in an essentially different manner, with respect to which we are for the present compelled to have recourse to pure hypothesis. Nor are the events subsequently taking place within the tissue-elements much better elucidated. The power of initiating fermentative processes, and of thus splitting up highly complex substances, in particular albuminous bodies, is very widely distributed in the cells of the most different organs; and the same cells possess the capa-

* Hoppe-Seyler, 'Pflüg. A.,' vii, p. 399; 'Physiolog. Chem.,' p. 930; Voit, 'Zeitschr. f. Biologie,' x, p. 218.

city of oxidizing the products of disintegration by means of the oxygen supplied them. Oxidation undoubtedly plays a very important part in the metabolism of the tissues; and it is indeed a universal rule that simpler combinations are yielded by the organs than were taken up by them. But the details of these oxidative processes, the intermediate steps between beginning and end, are, in almost all cases, hidden from us; nor are we better informed with regard to the possible syntheses, which may be of great importance, more especially in the renovation of tissues. The elucidation of these complicated events is a problem the solution of which is reserved almost altogether for the future, and which is all the more arduous as it must be attacked for each individual organ or tissue independently. For these events are by no means identical in every locality; rather it might be expected *a priori* that they would necessarily differ in character according to the functional effects to be secured by the chemical processses taking place in the various organs.

For it is by means of these processes that everything accomplished by the organism and its apparatus is carried out. This is true in the first place of the *secretions*. So far as it has been possible to trace them,* these always originate in the production by cells from their own protoplasm of the specific ingredients of the secretion; and on the removal, *i. e.* excretion, of the materials from the body, the protoplasm repairs its waste by making use of the substances supplied by the blood and lymph. Even when the required material is supplied in a prepared state to the gland by the transudation, as are the water and salts, or urea to the kidneys, secretion does not consist in a simple process of filtration or diffusion, for the materials first become integral parts of the cells before passing over into the secretion. In the second place, all the *movements* of the organism are the result of chemical processes—not merely the molecular movements, *i. e.* animal heat, but also those carried out by the contractile substance of the smooth and striped muscle-fibres and the contractile cell-protoplasm. Thirdly and lastly, *the growth of the body, from first to last, and the regeneration and new formation of its*

* Cf. the exhaustive exposition by Heidenhain in Hermann's 'Hdb. d. Physiol.,' v, I.

parts depend only and solely on chemical processes. For there is no mode in which new elements can arise except by the existing older cells taking up the material presented to them, assimilating it, so increasing in size, and out of themselves producing new elementary parts. The material is obtained from the blood-stream or transudation after that period of embryonic life at least in which the heart and circulation are established; and so abundant is the supply during the period of growth that the production of elements and tissues is then constantly in excess of what is needed to replace the worn-out parts. But I need hardly say that new formation and regeneration do not terminate with the end of the growing period. They continue throughout life, though with an amount of vigour differing greatly in the various organs and tissues, and it is invariably the same, though almost completely unknown, chemical processes, by whose agency it becomes possible for the ingredients of the blood-transudation to be transformed into the specific constituents of the various tissues.

Precisely the activities of the third category are of chief interest, if we seek to discover the conditions under which the normal constitution of the organs is maintained. It is true, as you will bear in mind, that the nature of the animal organism and its mechanism absolutely forbids the drawing of any sharp distinction between the so-called "work done" in a strict sense—secretion and movement—and regeneration. For *both of these go hand in hand* during the whole course of the vital manifestations. No work is done by the organism without the regeneration of the tissues being at the same time promoted; and, on the other hand, from the renovation of the tissues there almost invariably accrues some additional advantage to the organism—something is done towards meeting its general requirements. This is most clearly seen in the case of the secretions which, as has been shown, are produced at the expense of the constituent elements of the glands concerned. If the *sebum* be the product of the fatty degeneration of the exuberant epithelium of the sebaceous glands, if the *mucus* of certain mucous glands arises from the local mucous metaplasia of some of the secretory cells, the secretion of sebum and mucus must constantly involve a destruction and immediately succeeding

regeneration of these cells—since we never fail to find cells in the sebaceous and mucous glands. The same holds good essentially of most of the remaining glands, even though their constituent cells do not perish as such, or become in any way destroyed during secretion. For since the production of the specific material of secretion takes place without exception at the cost of the cell-protoplasm, there occurs here too *pari passu* with the secretion a continuous waste and renovation of the cell-substance. Nor is it possible, in the spleen, lymphatic glands, and bone-marrow, to separate the hæmapoietic function from the never-ceasing renovation of these organs. With respect to the muscles and some of the glands, *e. g.* the liver, our knowledge of the morphological changes occurring in their elementary parts during the period of functional activity is far too meagre to allow of our giving a definite opinion as to the extent and amount of waste and repair which may take place there. It is, however, certain that the muscle-fibres and hepatic cells are not stable apparatus which, as Hoppe expresses it, work up the nutrient materials supplied them in the manner of a machine. Rather the work is done at the expense of their own substance; and although the organic form of the fibre or cell is probably preserved, there is no doubt that the contents are altered and renovated during, and in consequence of, work.

The examples above cited may, some of them at least, at the same time serve as evidence for the converse proposition, that whenever regeneration takes place something is also accomplished for the benefit of the organism as a whole. The sebaceous glands, the spleen and lymphatic glands, might indeed have been more properly referred to in this connection, since, so far as we know, the processes in which they are engaged proceed uninterruptedly throughout life; there takes place in them, independently of all other influences, an incessant consumption and renovation of elements, and what they furnish is a gain, a service to the organism. A gain of this kind must of necessity result from all renovative processes, inasmuch as the used-up materials are turned over to the juices of the body, and can then be further utilised; to this rule there is at most one exception—direct expulsion to which, *e. g.* the horny portions of the epidermis are subject.

It is therefore unnecessary to recur to the heat, which is undoubtedly produced, though in small quantities, in all new formation and regeneration, before recognising *in this indissoluble connection between the various activities, more especially between the so-called work done* (*in a strict sense*) *and the renovative processes of the organs and tissues* one of the most characteristic peculiarities of animal life. This connection must be ever present to the mind of him who desires to gain an insight into the processes on which the physiology and pathology of nutrition depend. While life lasts the organism never ceases to produce heat, to carry out movements, and to accomplish various other kinds of work; and just as little does the continuous waste and repair of the tissues ever come to an end. The activity with which this renovation takes place is marked by the greatest imaginable differences in the various organs, and even in various parts of the same organ; but no portion of the living body is absolutely stable. Our knowledge, more or less accurate, of the chemical processes and morphological changes involved in the consumption, the destruction of the constituent elements is limited, as already noticed, to certain organs; while as regards the regenerative processes our positive information is, if possible, still more scanty—a statement which will not surprise you after the examples which have been adduced. So much we know, however, that they are most intimately bound up with the needs of the organism and the work done. The strict economy prevailing throughout all the arrangements of the animal organism is very strikingly noticeable here. The physiological body retains nothing superfluous, nothing except what subserves the good of the whole. The cells of the thymus are no longer replaced from the moment when other organs undertake for the body what was previously done by it; and the callus after a fracture disappears in so far as it is unnecessary for stability.

From these considerations it seems to me to follow as a direct inference that for the maintenance of the organs and tissues in their normal state and constitution *the regular circulation of blood of normal quality, and the physiological activity of the organs, i. e.* of their constituent elements, *are equally necessary.* The circulating blood conveys to the

tissues the solid, fluid, and gaseous ingredients required for their metabolism. In the absence of circulating blood it is obviously impossible for a renovation of the used-up and waste tissue to take place; and if the blood arriving in the organ be too small in quantity or faulty in composition, the chemical processes occurring in the tissues and their cells must undoubtedly suffer as the result. Yet it does not at once follow that a very abundant supply of normal blood will be attended by a correspondingly increased metabolism of all the organs. It is necessary in addition that these organs should first of all be capable, and then, if I may so say, stimulated and induced to elaborate more material; without the simultaneous increase of cell-activity an increased supply of material is useless to the organs. But should you ask how the cellular elements are stimulated and set in action, it would be necessary for me, did I wish to make my answer in any measure satisfactory, to enter upon a consideration of the causes of life. For it is impossible to avoid representing to our minds the animal cells as being during life in a state of incessant internal motion, though very variable in degree, the ultimate impulse to which eludes recognition. Especially in dealing with the whole subject of growth proper, we cannot, as I shall show more particularly afterwards, dispense with the assumption of a capacity inherent in the germ-cells from the first and transmitted by inheritance; if for no other reason because only in this way can the extreme inequality in the growth of the various organs, both as regards duration and intensity, be made intelligible. It is not, on the other hand, in any way opposed to this hypothesis that the *amount* of internal motion, *i. e.* of cell-activity, varies within certain limits even under normal conditions. In *some* tissues indeed the energy of the cell-metabolism appears up to a certain point to increase or decrease with the supply. Yet this holds good only of a limited group, as probably the connective tissues, the epidermis, and others—in a sense, also, of some glands; such a view would be most erroneous if applied to the great majority of the organs, more especially to those which we are accustomed to regard as working organs proper. Their metabolism is very much more influenced by another factor, namely, the *nervous system*.

You all know that the activity of the striped muscles, and in all probability of the unstriped as well, is not merely controlled by the nervous system, but is also, in normal conditions, initiated solely by nervous influence, so that no muscle contracts except its nerve be stimulated. The case is precisely similar with the secretion of many glands, as the salivary, lachrymal, sweat-glands, and pancreas; and though the remaining digestive glands and some others have not yet been proved to be similarly dependent on nervous influence, there are many circumstances making in favour of their identity in this particular. At any rate it is nervous influence which here, as in all muscles and the above-mentioned glands, supplies by means of the dilated arteries the larger quantity of material required for work. Muscles and glands afford, accordingly, the most striking illustrations of how the nervous system participates in the most direct manner in the chemical processes taking place within the tissue-elements. But if, in addition, the constitution and condition of the muscles and glands are altered by the chemical processes taking place in them during their active period, a mere reference to the fact suffices to show that the question, so often raised and vigorously disputed, of the existence of *trophic nerves* is, when put so broadly, an idle one. Every motor or secretory nerve is at the same time a trophic one, in so far as it decidedly plays a part in the metabolism, and hence in the nutrition, of muscles and glands. Yet in reality, the whole discussion turns, not on this point, but on whether, in addition, and without regard, to the work done, the remaining vital activities of the cells are also controlled by the nervous system, or, in other words, on whether those chemical processes in the tissue-elements, by which strictly speaking no work is accomplished, are dependent on the nervous system or regulated by it.

Certainly anyone who bears in mind the extraordinary differences in the innervation of the various tissues, and considers further what complications appear at every step in investigating the functions of the animal organism, will hardly expect a simple affirmative or negative answer to this question. The elementary parts of some organs and tissues are so intimately connected with the nerves as that the latter

terminate in them; in other organs such a connection is altogether out of the question. Are we really to believe that this distinct distribution in each case is a perfectly immaterial circumstance? Please remember, on the other hand, that when innervation is destroyed, not only are the sensibility and mobility of a part abolished, but the circulation through it suffers severely,—a disturbance which, at least in superficial parts, cannot be without an injurious effect on their temperature,—and you will, I think, admit that we are sufficiently warned to exercise foresight in interpreting the phenomena following disturbances of innervation.

Let us now examine with all reserve the clinical and experimental facts brought forward by writers in proof of the existence and influence of trophic nerves, facts which, I cannot help feeling, are very unequal in importance. Of the *nerves* we have long known that when their continuity is interrupted, *their peripheral portions regularly atrophy.* But with regard to the voluntary muscles also, a large number of facts, in my opinion convincing, have been accumulated in the last ten years, all tending to prove that they fall a prey to atrophy, occasionally of a very marked character, when their nervous connection with the medulla is severed. Lastly, since the time of Bernard it has often been observed that the submaxillary gland of the dog is very much reduced in size after division of the *lingualis quinti* or even of one of its glandular branches. In these cases, about which I shall speak more particularly in the chapter on atrophy, the exercise of *a true and undoubted trophic influence by certain nerves and nerve-centres* cannot be called in question. But, as you will notice, here again we are concerned, in addition to the nerves themselves, with muscles and glands, *i. e.* with parts that, morphologically and functionally, are so intimately bound up with the nerves that they may to a certain extent be regarded as their end-organs. Hence the conclusions drawn from them cannot be simply applied to the remaining organs and tissues. What, then, is the position of the latter as regards the assumed trophic nerve-influences?

The facts usually cited in proof of the existence of such are very numerous and diversified, and have been accumulated in part as the result of experiments on animals and in

part by clinical observations on man. Let us take the experimental facts first; among them we shall find some which are well known to us from former discussions. These are the occurrence of *pneumonia* after division of the vagi in the rabbit; further, the keratitis and progressive panophthalmitis appearing after intracranial section of the trigeminus, and so often accompanied by ulceration of the lips and mouth; here belong too the excoriations and deep ulcers occurring in the paws of animals in whom the sciatic has been divided. The influence which—disregarding these more acute affections—the enervation of a part exerts on its growth and nutrition has been studied more especially by Schiff;* further by Vulpian,† Mantegazza,‡ H. Nasse,§ and others. As regards the growth of bone it has been made out by various observers that, after division of all the nerves of an extremity, the bones of an adult animal become thinner and more flexible, while in growing animals, on the contrary, they become thicker and often actually hypertrophied. With these results the statements of A. Bidder|| and Stirling¶ would be in harmony. According to them division of the cervical sympathetic in young rabbits is followed by increased growth on the same side. If only the *fact* were better established! But other experimenters, and I myself among them, have never been able to feel convinced that such intensified growth really results from section of the sympathetic. It is at most in epidermoid structures, more especially in the hairs, that increased growth appears to have been regularly observed. Hyperplasia of the popliteal or inguinal *lymphatic glands* has moreover been repeatedly noticed after division of the sciatic.‡ On the other hand, section of the nerves passing to the *comb* of the cock and to the *wattles* on the throat of the turkey-cock is attended by marked *atrophy* of these structures. Lastly, there is contained in the literature of the subject a

* Schiff, 'Compt. rend.,' 1854, p. 1050; 'Untersuchung. z. Physiol. d. Nervensystems,' 1855, p. 166; 'Leçons sur la physiol. de la digestion,' ii, p. 539, 1867.

† Vulpian, 'Leçons sur l'appareil vasomot.,' ii, p. 352, 1875.

‡ Mantegazza, 'Gaz. méd. Lomb.,' 1865, No. 33, 1867, No. 18.

§ H. Nasse, 'Pflüg. A.,' xxiii, p. 361.

|| A. Bidder, 'Ctbl. f. Chir.,' 1874, No. 7.

¶ Stirling, 'Journ. of Anat. and Physiol.,' x, p. 511, 1876.

communication by Obolensky,*—unfortunately, however, only a preliminary one—according to which division of the nerves in the spermatic cord results in extreme atrophy of the testicle on the same side. I am not aware whether this observation has been confirmed by other writers.

The facts, bearing on this subject, derived from human pathology, are no less varied; and by no one have they been followed up and collected with greater care than by Charcot.† Here too a number of *inflammatory* affections occupy the chief place; as *erythema*, the *wheals of urticaria, pemphigus*, and especially *herpes*,—affections whose connection locally and in point of time with certain nervous excitations long ago attracted the notice of physicians. But in proof that inflammations having a nervous basis are not restricted to the skin, Charcot appeals to the *cystitis* and *pyelitis* met with in disease of the spinal cord. In addition to these inflammatory affections he cites certain cutaneous changes following wounds of nerves, which were specially studied in the American Civil War,‡ though with us too they are not uncommonly observed. The skin, more particularly of the fingers and toes, becomes thin as paper, and at the same time smooth and shining; or the epidermis scales off in quantity, while the nails grow jagged and abnormally curved; the growth of the hair is also affected, becoming either scantier or more luxuriant. Charcot believes further that certain chronic processes, partly inflammatory and partly atrophic, met with in the *joints* and *bones* of extremities, the muscles of which atrophy through spinal causes, should be referred to deranged trophic innervation of these parts of the skeleton. Finally, he attaches special importance to certain cases of *decubitus*, the development of which is extremely acute and which extend very rapidly. The sores have been repeatedly observed by himself

* Obolensky, 'Med. Ctbl.,' 1867, p. 497.

† Charcot, 'Mouvem. méd.,' 1870, Nos. 24—33; 'Klin. Vorträge über Krankheiten des Nervensystems,' übers v. Feltzer, Stuttgart, 1874, p. 1; Conyba, 'Des troubles trophiques consécutifs aux lésions traumatiques de la moëlle et des nerfs,' Paris, 1871.

‡ Weir Mitchell, Morehouse, and Keen, 'Gun-shot Wounds and other Injuries of the Nerves,' Philad., 1864; Weir Mitchell, 'Injuries of Nerves and their Consequences,' Philad., 1872; cf. also Leyden, 'Klinik der Rückenmarkskrankh.,' i, p. 153; Erb, in 'Ziemssen's Hdb.,' xi, 2, Abth. 1, p. 112.

and others in cerebral and spinal hæmorrhage or other focal affections destructive of continuity, in some instances exactly in the middle line over the sacrum, and in others, when the disease was unilateral, confined to the paralysed side.

But the great diversity in the nature of these disturbances must, it seems to me, prove rather startling to an unbiassed person. Can injury of the same nerves give rise on one occasion to inflammation, on another to atrophy; at one time to thickening and hypertrophy, and at another to complete necrosis, gangrene? This is not made more credible by seeking, with Charcot, the determining factor, *not in an interruption or cessation of activity on the part of the trophic nerves*, but, on the contrary, in *an increased action, a stimulation of them*. Moreover, the experimental basis of the view consists solely in some worthless experiments of Samuel,* the incorrectness of which has long ago been proved. But on more nearly examining all the experimental and clinical facts that have been brought forward in support of the doctrine of trophic nervous influences, it will at once be seen that a large number of them are absolutely valueless for the decision of our question. This applies to the vagus pneumonia and trigeminus keratitis, whose mode of origin, you will remember, was easily understood without any necessity for calling in unknown nervous actions. And it is true no less of the ulcerations of the lips or paws after section of the trigeminus or sciatic; these are caused simply by the wounding of the anæsthetic buccal mucous membrane by the animals' teeth and by the failure, owing to the absence of sensibility, to guard against injuries to the feet. Further, with respect to the cystitis and pyelitis, I shall, when dealing with the pathology of the urinary organs, offer proof that these affections are always due to infective organisms, conveyed into the bladder from without, and are therefore only very indirectly connected with the disturbed innervation. Lastly, as regards the neurotic inflammations of the skin in human pathology, it is at least doubtful whether the erythemas and urticaria are at all inflammatory, and not simply vaso-dilator phenomena; and although the inflammatory

* Samuel, 'D. trophischen Nerven,' Leipz., 1860; Tobias, 'Virch. A.,' xxiv, p. 579.

nature of the herpes- and pemphigus-vesicles cannot be denied, still we are now sufficiently well acquainted with the minute characters of inflammation to look on them as anything rather than evidence of trophic nervous influence. It is when regarded from this standpoint that the inflammatory joint-affections of tabes are robbed of all significance as evidence for Charcot's view—even though we are not yet in a position to explain their unusual frequency in this disease. Evidence, to be really demonstrative of the existence of trophic nerve-influences, can properly consist only of *alterations* or *derangements of nutrition, which can be shown to be directly dependent on the quiescence or stimulation of definite nervous tracts.* But the prospect of establishing this dependence is not at present a particularly brilliant one.

Enlargement of the lymphatic glands of the leg after section of the sciatic—apparently beyond all question a disturbance of nutrition—is stated by Tizzone* to be absent if proper precautions are taken to protect the extremity from injury and prevent ulceration of the paw. But our chief difficulty in coming to a conclusion is owing to the fact that in none of the experimental or clinical cases is the simultaneous participation of nerves of another category, especially of the vessel-nerves, excluded. Thus there is no doubt whatever that the atrophy of the cock's comb and of the wattles is attributable simply to the division the vaso-dilators, and their consequent deprival of the ampler supply of blood which they at least occasionally require. Should the statements of Obolensky—which so far as I know are unsupported by clinical experience—be correct, we cannot avoid placing the testicles by the side of the muscles and submaxillary gland as having the same trophic relation to the nervous system. The peculiar position of the muscles and submaxillary gland we have already recognised, and shall enter more particularly into the proofs of it later on. But with the glossy skin it is quite a different matter. The alterations which the skin of the fingers and, eventually, of the whole hand, sustain on division of the median or ulnar are, it is true, striking enough; but who will say how much of this is due to the circulatory disturbance and consecutive change of tempera-

* Tizzone, 'Arch. per le Scienze Med.,' iv, Fasc. 1, 1879.

ture, or to the anæsthesia and its consequences? Who would venture to pronounce, further, how large a part of the alterations in the joints or bones depends only and solely on deranged mobility and muscular atrophy? Very little can be made out of the *acute decubitus* even. I admit, of course, that these cases are distinguished from the ordinary mortification due to pressure by the rapidity of their development and the malignancy of their course, and more especially by their appearing despite the utmost care to protect against all injuries. Nevertheless these are mostly, if I may say so, quantitative differences, differences of degree; and with the best intention, I fail to find therein such a fundamental departure from the causes and history of common decubitus (to be soon explained) as to need for its elucidation the setting up of a new, and, moreover, so far-reaching a factor. Such reserve appears to me to be enjoined so long as there is no real precision in connecting the cerebral or spinal diseases with the acute decubitus, *i. e.* so long as it has neither been shown which part of the nervous system is the determining one, nor the modus cleared up by which nervous influence, or its abeyance, can in so brief a period bring about the death of large portions of skin, superficial fat, &c.

After all that has been said, you will grant, I think, that the evidence brought forward up to the present is too imperfect to admit of our inferring therefrom either the existence of trophic nerves or the importance of trophic nervous influence for the nutrition of the organs and tissues in general. To dispute the facts on which the statements of so excellent an observer as Charcot are based does not, of course, occur to me; and there is no one less inclined than myself to question the right of neuro-pathologists to speak of trophic disturbances in their clinical histories. When the skin is thin as paper, the nails fissured, and the hair-growth deficient; when the bones are abnormally fragile, and the articular cartilages atrophied; still more when entire portions of tissue become necrotic, these of course constitute disturbances of the nutrition of the part, *i. e.* trophic disturbances; and certainly the clinicians are right in applying the same name to all these changes. Nor do I think I am mistaken in supposing that the majority of German clinicians at least do

not mean to express anything else by the term "trophic disturbances"—always excepting the nerves, muscles, and certain glands. With respect to the remaining organs and tissues, however, the facts above mentioned are not at present of any appreciable service in helping us to understand their nutritive processes. The facts lie too far beyond the limits of our knowlege and conceptions of tissue-metabolism; and although we cannot, of course, ignore them, we are far from justified in drawing far-reaching conclusions from them with respect to the nutrition of all tissues and organs. To me at least it appears that we shall best secure ourselves against grievous error by departing as little as possible from the firm foundation of physiological experience; and we should therefore, when discussing pathological nutritive processes, avoid calling in the action of the nervous system, except where its participation is comprehensible and transparent to us. *Normal circulation and normal action of the cells*—this term being used to cover all the elementary parts of the various organs of the body—are the essential conditions to be fulfilled in order that the organs and tissues may be maintained in a physiological condition. Besides these, our positive knowledge extends to a third only, namely the maintenance of the *normal temperature* of the organism, *i. e.* of a temperature that varies only very slightly from 37·5° C. Such a temperature is indispensable if the multifarious chemical processes composing the total tissue-metabolism are to take place in a regular manner. This condition might therefore have been included under the second head, namely normal cell-activity; yet since it is so independent of the other factors controlling the physiological activity of the cells, it may legitimately be allotted a position to itself.

In accordance with these introductory remarks, the course to be pursued in this section—the Pathology of Nutrition—would appear to be naturally prescribed for us. The most obvious method, in fact, would be one analogous to that adopted in treating the Pathology of the Circulation. The pathology of nutrition is simply *the doctrine of nutrition under pathological conditions*, and our most *rational* course would unquestionably be to commence our discussion with the consideration of these conditions. We should then have to ex-

amine what influences alterations in the circulation, whether of the motion or constitution of the blood, exert on the metabolism of the organs; secondly, in what manner changes in cell-activity, conditioned either by abnormal functional action or defective stimulation or other cause, affect nutrition; and thirdly, how nutrition is influenced by alterations of bodily temperature. Yet, however plausible such a course undoubtedly is, we shall not go to work in this way, because iu so doing we should be inconvenienced by unavoidable repetition, but chiefly because our knowledge is still utterly inadequate to such a method. Only in a few portions of this section can we with certainty perceive the connection of cause and effect. For by far the greater number of nutritive disturbances a satisfactory theory has still to be found; and, as so often happens in pathology, we must mainly content ourselves with laying down the facts. We should, at least, take facts as the starting-point of our discussion; and we shall, instead of adopting the rational method above indicated, pursue an opposite course and append to the facts an inquiry into the possible or probable conditions.*

* Virchow, 'Hdb.,' i, p. 271; further, as the chief source of information for the whole section, 'D. Cellular-Pathologie,' Berlin, 4 Aufl., 1871; C. O. Weber, 'Handb.,' i, p. 240; Perls, 'Allg. Pathol.,' i, p. 146, 1877.

CHAPTER I.

LOCAL DEATH, NECROSIS.

*Causes of gangrene.—*1. *Extinction of the circulation.—Capillary stasis.—*2. *Disorganisation of the tissue-cells by chemical and traumatic, as well as by infective, agencies.—*3. *Interruption of tissue-metabolism due to abnormal temperature.—Unequal powers of resistance of the tissues against necrosive agencies.—Senile gangrene.—Spontaneous gangrene.—Gangræna per decubitum.—Yellow softening of the brain in aged persons.—Noma.—Gangrene due to ergotism.—Gangrene in anæsthetic parts.—Gangrene in diabetes mellitus.*

Forms in which necrosis is manifested.—Apparent integrity.—Withering, mummification.—Coagulation-necrosis.—Caseation.—Colliquation.—Gangræna humida and emphysematosa.—Mould-formation.—Fœtus papyraceus et maceratus.—Microscopic appearance of necrotic parts.—Disappearance of nuclei.—Symptoms of gangrene.

Circumscribed and diffuse gangrene.—Demarcation.—Reactive inflammation.—Variable course of the latter.—Encapsuling of the sequestrum.—Dissection by purulent inflammation.—Ulcers.—Their classification and course.—Vessel-diabrosis.—Putrid intoxication.—Davaine's septicæmia.

Diphtheria.—Description of the pseudo-membrane.—Croup, diphtheria, and diphtheritic croup.—Interpretation of the process.—Shedding of the pseudo-membrane.—Causes of diphtheria.—Diphtheria from corrosives and from pressure.—Infective diphtheria.—Diphtheria of wound-surfaces.—Diphtheroid foci.

WE commence the pathology of nutrition with an extreme —the *extinction of the metabolic processes in a part,* or as it

is termed, *local necrosis, gangrene*—because here the problem presents itself under, comparatively speaking, its simplest aspects. The conditions involving the destruction of a part may be directly inferred from our introductory discussion. For if (1) the circulation, (2) the action of the cells, (3) an approximately normal temperature are together necessary to its nutrition, its metabolism must be extinguished, and the death of the part ensue; if (1) *the circulation through it ceases,* (2) *if the functional activity of the tissue-cells is destroyed,* and (3) *if the temperature of the part is very considerably removed from the normal.* The etiology of necrosis can, accordingly, be conveniently arranged under various heads; though, as you will learn, the different categories may be combined in individual cases.

The circumstances in which the blood-supply of a part fails, or *the circulation through it ceases,* are well known to you. Anything that interrupts the flow of blood in the arteries distributed to a part, as *e. g.* thrombosis and embolism, compression from without by a ligature, tumour, inflammatory exudation, or purulent effusion—obviously renders the continuance of the circulation through the part impossible, unless compensation take place by means of collateral branches. The same effect attends complete interruption of the venous efflux, after this has persisted for a time without the development of collaterals. Hence complete interruption of the circulation is extremely rare after extensive venous thrombosis,* but much more readily ensues on strangulation and incarceration as well as on ligature of an entire part. The prejudicial agent may, in the last place, directly affect the capillary stream. Pressure to which the part is subjected from without, or also, if I may so say, an internal compression, such as results from the interstitial growth of tumours between the capillaries, may sometimes so seriously impede the blood-stream as to cause complete stagnation. Here too belongs the whole subject of so-called *stasis, i. e.* the irremediable stand-still of the blood in the capillaries—a subject which, it is true, has not the same interest for pathologists at present as attached to it some decades ago. For to us stasis means nothing but *stand-still with coagulation of the*

* Hueter, 'Virch. A.,' xvii, p. 482.

blood, whether, as ordinarily happens, the latter takes place by the fibrin-generators uniting, or as the result of some profound chemical changes. That actual thrombosis of the capillaries occurs only when their walls are necrosed has been already shown (p. 187). Such necrosis of the capillary walls may, under certain circumstances, develop uncomplicated by other change, *e.g.* after absolute arterial ischæmia of long duration, or in progressive gangrene—of which more anon. Very frequently, however, there take place *pari passu* with the necrosis certain alterations of the contents of the capillaries, *i. e.* of the blood circulating in them. When a capillary area is subjected from any cause to greatly increased evaporation, the walls of the capillaries will die after a time, and the blood contained in them dry up, especially if conditions that abnormally retard the capillary stream are also present. An abnormal degree of heat kills the walls, but it also coagulates the blood in the capillaries. Chemically different substances must not only injure the capillary walls more or less, but also, according to their character, alter the liquor sanguinis and blood-corpuscles. Whether a separation of the serum-albumen, or a solution, or perhaps shrinking, of the blood-corpuscles then takes place, chiefly depends on the nature of the chemical agent, or its concentration. In all this, I need hardly say, the laws of diffusion play an essential part; and it is therefore not surprising that a substance sometimes affects the blood or the blood-corpuscles more strongly than the capillary membrane. When this is the case—and it is most easily conceivable of very fugitive agencies—a stasis so originating could most likely pass off, or, as it is termed, be resolved; the coagulum consisting of blood or blood-corpuscles being swept away by the blood-stream, and the circulation re-established in the capillaries whose vitality has not suffered. The portion of blood which had been involved in the stasis would, it is true, then also be definitively lost to the circulation. None of these facts, which were long since established by the careful experimental researches of H. Weber* and others, and have been studied

* H. Weber, Müller's 'Arch. f. Anat. u. Phys.,' 1852, p. 361; Schuler, 'Verhdl. d. Würzb. phys. med. Ges.,' 1854, p. 248.

afresh by C. Hueter,* present any difficulty to the understanding. Their importance in pathology, however, consists in this—that, with the exception of the possibility of a restoration just referred to, the actual *true stasis always involves a permanent and irreparable cessation of the capillary circulation of the part.* Therein lies the fundamental difference as compared with *stagnation,* to which reference was made on a former occasion (p. 258). Stagnant blood, whether the flow be minimal, or even zero, is always *fluid ;* the stagnation may at any moment give place, on the removal of the cause, to an ordinary flow, while stasis, on the contrary, is definitive. Stagnant blood is indistinguishable in all essential characters from that of the rest of the circulation ; where stasis exists, the blood is always more or less profoundly altered. That stagnation may under certain circumstances pass into stasis is self-evident ; every inflammation causing necrosis affords a most vivid illustration of the fact.

Of the influences which produce stasis some are at the same time adapted by their nature to so *disorganise* the cells of a part as to lead to the utter destruction of the function of the latter. In fact, chemical agencies as well as dessication, scalding, &c., usually affect not merely the capillaries, but also the tissue-elements supplied by them, simply because cells and vessels are in most regions intimately interspersed the one through the other. Yet it is not so in all localities. If you cauterise a mucous membrane with caustic potash you are equally certain to kill the vessels of the part in question and the epithelium and mucous tissue proper. But you may apply the caustic to the cornea over a considerable extent of surface and penetrate to a considerable depth without affecting one of its nutrient vessels ; and in the skin too it is not difficult to so manage that the epidermis alone shall be involved. It is also conceivable that, in a very susceptible tissue, the elements might be irreparably destroyed by a chemical substance, and the circulation not be impaired to the same extent. Thus Kussmaul† observed that on injecting a few drops of chloroform into the vessels of a rabbit's hind leg the whole of the muscles of the limb

* C. Hueter, 'D. Arch. f. klin. Chir.,' iv, pp. 105, 330.

† Kussmaul, 'Virch. A.,' xiii, p. 289.

become rigid and then die, while the circulation continues for hours, or even days, till the animal's death. A similar remark may be made with reference to severe traumata, such as *contusions* and *concussions* of parts. For these will also invariably involve the vessels of the locality affected; the vessels may, however, be more capable of resistance than the tissue-cells; and it must at any rate be admitted that the circulation of the part may be restored after the injury and still the part itself necrose because its elements are disorganised.

While the destruction of the life of the cell by corrosives is perhaps always due to chemical union between the substance of the cell and the injurious agent, or to the occurrence of some other profound chemical change which, like the dehydration or the coagulation of cell-albumen, is more or less clear to us, the same can unfortunately not be said of other influences by which the activity of the cell is terminated. I have here in mind certain *infective,* and in many cases undoubtedly *putrefactive,* actions which render the metabolic processes of the cells exposed to them absolutely impossible. When portions of tissue come into contact with decomposing urine, with putrid organic substances, or with offensive wound secretions, they usually die with more or less rapidity and to a greater or less extent. This very often happens indirectly as the result of inflammation going on to necrosis. In many cases, however, the tissue coming in contact with such materials perishes immediately without passing through any special intermediate stages. It is as though these substances were endowed with a capacity *to inhibit* the physiological metabolic processes. To which of the components of the fluids and materials the power of destroying the metabolism should be ascribed cannot be precisely stated at present. The participation of *lowly organisms* is common to them all; and the idea that these have some hand in the mortification of the tissue-cells the more readily suggests itself, as *the necrosive action of isolated bacterial colonies has been certainly established in other cases.* If fluid containing bacteria be introduced into a punctured or incised wound of the rabbit's cornea there is formed at the circumference of the little focus, into which the wound

quickly transforms itself, an annular zone of necrosis; and with respect to the colonies of micrococci in ulcerative endocarditis, I formerly laid stress on the fact that they are quite commonly surrounded by a narrow border of dead tissue. I shall afterwards have to speak at greater length of these processes, which Weigert has investigated with special thoroughness.

The third factor from which we expected a complete cessation of the metabolic processes to result, namely, *abnormal temperature,* must operate in a somewhat extreme form, or at least for a considerable time, in order that the effect anticipated may ensue. On plunging the ear or the leg of a rabbit into hot water, or into a freezing mixture, and thus raising the temperature to 54°—58° C., or lowering it to −16° or −18° C., the part perishes irrecoverably, even though the specified temperature has been maintained only for a very short time. After warming to 46°—48° or cooling to −7° or −8° for several minutes, the worst that can happen is, as I formerly told you, an inflammation of the ear or leg; while if you keep the part in water at 42° or in a freezing-mixture at −1° or −2° for a few minutes, this will result only in a hyperæmia which passes off after a relatively short time. If, on the other hand, you let the leg remain for several hours at this moderate degree of heat or cold, the consequence will be a more or less extensive necrosis. This difference is easily explained. The really extreme temperatures prove directly injurious, either by coagulating the albumen or other action, to the tissue-cells on the one hand and to the vessels on the other, so that recovery becomes impossible. Not so when the departure from the normal warmth is but slight, for the irritability of a frozen muscle is restored on thawing. Many circumstances conspire, however, to make less extreme changes of temperature destructive when they last longer. In the first place the circulation suffers therefrom, as will be most apparent to you of cold; and that such temperatures are not altogether indifferent, so far as the constitution of the cells is concerned, may be confidently anticipated; although the nature of the cell-change is not everywhere known. But the important point is that, when these abnormal tempera-

tures are present, the metabolism either does not proceed at all, or takes place in such irregular fashion as to be incompatible with the continued life of the parts. This circumstance explains how a moderate deviation of temperature of comparatively short duration is deleterious to some tissues and organs, while others must be exposed for a much longer period before they are destroyed. A loop of intestine, if subjected for a couple of hours to a temperature of 8—10° C. is certain to perish, while the effect of such exposure on the muscles, and still more the skin, is *nil* or very inconsiderable.

In the foregoing classification and exposition of the etiology of necrosis we naturally assumed that we were dealing with parts of the body in which the conditions of normal nutrition, collectively and individually, were previously fulfilled in a regular manner. But in this connection some special factors must be given due weight. I do not refer so much to the circumstance that several causes from the different categories frequently combine in producing necrosis. I gave you examples of such combination when speaking just now of the influence of extreme temperatures, and a moment's reflection will show that it must occur pretty often. You have learned that vessels which pass through a necrotic tissue undergo thrombosis; hence there may be some difficulty in subsequently determining the actual cause of the gangrene, and not only so, but a primary necrosis in one place may even set up a secondary necrosis in its neighbourhood. Another more important factor than these—the analysis of which depends on simple principles—is of moment in the etiology of gangrene, and had to be considered already in connection with necrosis from heat and cold; this is the *extremely unequal tenacity of life*, or, better expressed, *resisting power, of the various tissues to influences favouring mortification.* A part which is completely deprived of its blood-supply dies: to this rule there is no exception; but while one part succumbs to necrosis very soon after the circulation has ceased, another does not do so till very much later on. If you inquire how the setting-in of cell-death is to be recognised, it must be confessed that all the signs which depend upon non-performance of function are misleading, because they might with

equal justice be referred to the absence of a circulation; this applies to sensibility, and in superficial parts to temperature. We have, however, a very certain reagent for the necrosis due to interruption of the blood-supply, namely the possibility or impossibility of recovery, of the renewed vitality of the part, on the re-establishment of the circulation. The various organs display the greatest possible differences in this respect. Portions of the brain, the kidney, the intestine very quickly succumb—certainly within one or two hours—after cutting off the blood-supply, while the skin and the muscles can altogether dispense with a circulation for as much as ten to twelve hours or more, and still retain their capacity of carrying on the metabolic processes. This is partly attributable, no doubt, to the unequal resisting powers of the vessels of the various organs towards anæmia; but the chief factor is certainly the *respective degrees of sensitiveness of their elementary parts*. Has not Litten* shown that ligature of the a. renalis in rabbits, for from one and a half to two hours, is sufficient to produce, on removal of the ligature, a necrosis involving the greatest part of the epithelium of the convoluted tubes, although the circulation becomes perfectly, and, it would appear, permanently re-established through the whole of the renal vessels. Similar diversities of behaviour are displayed by the various tissues towards the necrosive influences of the second category. They depend in part on very evident differences in the constitution of the tissues, such as their unequal toughness or elasticity, so that, *e. g.* a diffused force which would inevitably give rise to mortification of parts of the brain proves harmless to the skin, connective tissue, and still more to bone. The extreme sensitiveness of the cerebral substance to loss of water has also long been known to surgeons.

But this factor, this power of resisting necrosive influences, plays a still more important part in pathology. In order that a part whose cells are possessed of vitality and average functional capacity may die, the circulation must be completely interrupted for a period more or less long; and, on the other hand, if a part have a regular circulation, it is necessary, to the production of mortification, that the chemical or mechanical

* Litten, 'Ztschr. f. klin. Med.,' i, Heft 1.

disorganising influences shall be of no inconsiderable strength. What happens when one of these conditions is *not perfectly fulfilled,* when the circulation of a part is feeble or defective, when the organisation of the cells is faulty or their functional power impaired? Now the result is in fact one that might easily be inferred *a priori;* for in such circumstances *much slighter noxæ of one category or the other will suffice to produce gangrene.* Opportunities for verifying this rule by experiment or experience are, as will readily be understood, abundant. For every anæmia of general, and more especially of local origin, every venous stagnation, every circulatory disturbance depending on inflammation involves, of course, a defective or inadequate circulation through the part affected; and by testing the behaviour of anæmic, congested, or inflamed parts towards mechanical, chemical, or thermal injury, we can easily get information on the point now under consideration. If the ear of a rabbit be made highly anæmic by ligaturing the corresponding carotid and auricularis posterior, and then be placed in hot water, a slighter degree of heat or a much shorter period suffices to bring about gangrene of the ear. Paint an ear so rendered anæmic with croton-oil, and there not uncommonly ensues, instead of inflammation, a more or less extensive necrosis; or, at least, the inflammation will terminate in necrosis.* This effect is no doubt partially due in both cases to the death of the vessels, which are themselves living cellular structures; they die, instead of becoming inflamed, and stasis sets in in consequence. Nevertheless the reduced functional power of the tissue-elements resulting from the circulatory disturbance must assuredly not be under-estimated as a co-operating factor. Human pathology, however, supplies us with much more striking examples. That severe inflammations often issue in gangrene you know from our earlier discussions (p. 337); and you remember that one of the causes of this is the continued presence of the exciter of inflammation. But what does this imply if not that the same noxa which sets up inflammation in a part with a normal circulation causes its necrosis when the circulation is defective? This does not merely hold of inflammatory derangements of the circu-

* Samuel, 'Med. Ctbl.,' 1868, p. 401; 'Virch. A.,' xl, p. 213, xliii, p. 552.

lation; it is possible for a local circulatory disturbance which in perfectly healthy persons would be really trifling or attended by insignificant results, such as thrombosis of a vein, to produce gangrene in patients whose circulation is abnormal owing to fatty heart or to some other affection of the heart or lungs. In such a patient I lately saw extensive yellow softening of the left cerebral hemisphere, especially of the temporo-sphenoidal lobe, for which no cause could be discovered except extreme sclerotic narrowing of the vertebral artery of the same side complicated by thrombosis at its origin. Nothing, however, throws so much light on these relations as two much-discussed and, with reason, greatly-dreaded morbid processes, *senile gangrene* and *decubitus.*

Senile gangrene appears in old persons who have long complained of numbness, with sensations of cold and tingling in the extremities. Its appearance is determined by very trifling violence—a slight bruise, the evulsion of an ingrowing nail; in short, by accidents which in a healthy individual would at most be attended by an insignificant inflammation. Instead of inflaming, the toe—for the lower extremities are the favourite seat of senile gangrene—becomes necrotic first, and thence the mortification spreads so that large portions of the limb, half or the whole foot, or even part of the leg, may be totally lost. In these cases there is almost without exception extreme sclerosis of the arteries of the extremities, by which the blood-supply to the leg, and particularly to the foot, is very seriously impeded. The circulation in the leg exactly suffices to maintain its vitality, although only with a certain prejudice to its physiological functions. It needs but a very slight injury to the tissue-cells to endanger still more their unstable equilibrium, and a trifling additional disturbance of the circulation to bring about the death of the vessel walls, and with it a deleterious stasis. Thrombosis of one or other of the arteries of the leg frequently complicates the sclerosis, but this is by no means necessary; and, at any rate, you will carefully distinguish between senile gangrene and the essentially thrombotic or *spontaneous gangrene,* as it is, strange to say, still called. For the latter is the effect of interrupting the blood-supply to an extremity in which both the circulation and the cellular elements were

previously quite normal and possessed of full vitality, and is, as might naturally be expected, most frequently brought about by embolism.

While it is a chronic circulatory disturbance that determines the unfavourable course of senile gangrene, we have in *mortification from pressure,* or *gangræna per decubitum,* to deal as a rule with much more acute processes. By *pressure-gangrene* is not to be understood that variety of necrosis which sometimes originates in perfectly healthy parts from excessive compression, *e. g.* owing to unskilfully applied bandages or an ill-fitting boot. Nor should the term be applied to every sore of a bed-ridden patient: to those, for example, which are due to gangrenous inflammation resulting from uncleanliness, where continued maceration of the epidermis in urine, or the discharges from wounds, or even liquid fæces, is allowed to take place. None of these forms of necrosis have any peculiar elements, and are the less deserving of special discussion as they regularly recover on removing the excessive pressure and keeping the patient clean—a most convincing demonstration of their origin. The term decubitus is applied exclusively to cases where the necrosis sets in as the result of what would in other circumstances be utterly inadequate causes, such as slight pressure from folds in the bed or coverings, slight uncleanliness, or wetting of the skin. The necrosis sometimes leads to extensive and deep destruction; but it appears only after the patient has been confined to bed for a considerable time, and even then not in every case, but only in those persons or parts—and this is the essential factor—in which the circulation is defective and inadequate. Two groups of diseases chiefly predispose to it. First of all, *paralytic conditions,* where the disturbance of vascular innervation so often accompanying paralysis is the source of the predisposition; and, second and more especially, those processes in whose course a *hypostatic congestion* is developed. You know what processes these are (p. 147): where weak heart co-exists with shallow respirations, and particularly with muscular feebleness, the danger of hypostatic congestion in dependent parts is ever present. Patients passing through a high fever of some duration, and those most of all who are prostrated by septic

and infective pyrexial processes, like pyæmia and typhoid, supply the chief contingent to decubitus; while if pyrexial affections set in in the paralysed, the risks to such patients are great. Necrosis from decubitus is usually very circumscribed at first; but when the circumstances favouring its origin continue in operation it steadily extends in area, attacks the deeper structures, and ultimately causes enormous losses of substance. Decubital gangrene selects by preference those localities where bony structures lie immediately beneath the skin, and where therefore pressure, even though slight, at once tells on the part. Such are the regions over the sacrum, trochanters, shoulder-blades, elbows, heels, ankles, and—owing to the anæmia—the tips of the toes. But the pressure of skin against skin may occasionally induce decubitus, as in the case of the scrotum, the labia, or the inguinal folds, especially when they have become œdematous from lasting circulatory disturbance.

For the converse proposition—that in cells whose organisation is defective or function feeble, a circulatory disturbance even of moderate severity may be followed by necrosis—a variety of proofs may easily be gathered from human pathology. There is no doubt that we have here one of the essential reasons why necrotic processes set in by preference in *aged* persons. I may remind you *e. g.* of the frequency of *yellow cerebral softening* in extreme old age. For part of the brain to die in a young man, its circulation must be completely interrupted, either by thrombosis, embolism, or compression of the vessel from without. In an aged person a simple arteriosclerosis, which, it is true, considerably diminishes, but by no means stops the circulation, is sufficient to gradually give rise to necrotic softening without the intercurrence of any additional special noxa. True, this is to be expected only in particularly delicate and sensitive tissues, to which class, as stated, the brain especially belongs. For the rest, it is possible that the shallow or deeper punctiform depressions, so often met with on the surface of the kidneys in old people, are to be similarly interpreted. When, however, the cell metabolism and nutrition of the tissues is from other causes much more weakened and defective even than would be natural in old age, then simple anæmia or ordinary in-

flammation may lead to grengrene of other organs and tissues, often of those whose powers of resistance are greatest. This is, I think, the most plausible explanation of the so-called *noma* or *water-canker*, a form of necrosis attacking by preference the face of children, but also other localities, *e. g.* the labia, and often rapidly involving the vicinity and destroying the soft parts widely and deeply. The starting-point of the entire process is usually an apparently trifling trauma, a small wound of the face or the like. But even if the notion of some writers, that bacteria have a share in its production, be correct, the essentially characteristic feature of the disease is nevertheless the extraordinary rapidity and malignancy with which the noma eats into the surrounding tissues; and this is undoubtedly attributable, as all observers are agreed, to their imperfect nutrition and the defective resisting power consequent upon it. For noma confines its attacks to such children as live under very unfavorable hygienic conditions, are insufficiently fed, or are specially enfeebled and reduced by having just passed through severe illness, such as scarlet or typhoid fever. A congenital defect in the organisation of the tissues also appears to favour its production, for the hereditary appearance of noma in certain families has been reported.

The same considerations are apparently applicable in all essential points to *ergotism*, a disease which at present is very rarely seen, but formed one of the scourges of the Middle Ages. This is an exquisitely typical form of poisoning that appeared epidemically amongst a population, only because very many persons had partaken of the poison, *i. e.* the ergot mixed with rye. As regards symptoms, it will be enough to mention here that individuals who had for a long period eaten bread containing ergot were attacked first by digestive disturbances, general feebleness and languor, vertigo and sleeplessness, then by itching or creeping sensations and numbness, alternating with pain in the extremities, and in extreme cases by twitchings and convulsions of the limbs. After all these conditions had lasted for a time, there appeared in some locality or other, usually the toes, a gangrene which quickly spread and destroyed large portions of the extremities, also attacking the nose and ears. The

interpretation of these necroses is uncertain, because, as already stated, owing to more careful cultivation of the soil, such severe ergotism no longer occurs in man, while the animals used in our experiments generally succumb to doses in no way comparable to those partaken of in the *itching disease,* as ergotism was also called. The most widely accepted view is that the ergotin causes spastic contraction of the smaller arteries, and that the resulting anæmia gives rise to necroses in individuals who are already badly nourished, and are in addition severely prostrated by the disease itself. If this theory be correct, we have in ergotism excellent evidence of the truth of the proposition with which we started; yet I must not conceal from you that the constricting action of ergotin on the vessels has recently been called in question. Zweifel* argues that the anæsthesia resulting from the ergot must alone be made answerable for the necrosis, and draws a parallel between this form of gangrene aud the traumatic necrosis of animals in whom the sciatic or the brachial plexus is divided, and who fail to guard against injuries to the leg, because they do not notice them.† For the rest, these traumatic necroses might in a certain sense be called in in support of our proposition, provided at least that the vessel-nerves are also divided by the neurotomy. For there is no doubt that the circulatory disturbance thus conditioned lowers the resisting powers of the tissues toward injury. As regards the cornea, Senftleben‡ was, nevertheless, able to determine positively that in order to produce necrosis of an eye made anæsthetic by division of the trigeminus it is necessary that a wound of the same severity be inflicted as is required to produce the same effect in the other sensitive eye; and as to the remaining analogous cases, there is no doubt that the dimensions of the gangrene are essentially dependent on the severity of the trauma. Still, I hesitate to accept an exclusive connection of this kind for gangrene due to ergotism. The very progress and invasion of new areas by the gangrene, as testified to by all observers, seems to

* Zweifel, 'Arch. f. exp. Path.,' iv, p. 287.

† Brown-Séquard, 'Compt. rend. de la soc. de Biol.,' i, 1849, p. 136; 'Exper. Researches applied to Phys. and Pathol.,' New York, 1853.

‡ Senftleben, 'Virch. A.,' lxv, p. 69.

me to make very clearly in favour of the belief that the anæsthesia is not at any rate the sole determining element, and that under all circumstances the chief importance attaches to the want of resisting power of the tissues.

To special pathology or to surgery must be left the task of analysing from the above points of view other varieties of gangrene, *e. g.* that occurring in *lepra mutilans* and so-called *symmetrical gangrene.* I desire only to direct your attention to one other remarkable circumstance, namely, the pronounced tendency to gangrene which is produced by a defective constitution of the blood. This applies in some degree to certain forms of general anæmia and still more to hydræmia, but it is most of all true of a disease in which the blood-stream presents no deviation whatever from the normal, the composition of the blood alone being altered, namely, *diabetes mellitus.* The diabetic suffer with remarkable frequency from gangrenous inflammation of the cellular tissue, so-called carbuncles; and trifling traumata, inflammation around the nails, slight bruises, chilblains and the like, only too easily cause necrosis in these patients. The explanation of this predisposition appears simple enough. I will certainly not deny that special relations of which we are still ignorant may also participate in it; but thus much may be accepted without hesitation—that the abnormally constituted blood exerts an influence on the metabolism both of the elements of the vessel walls and of the tissue-cells proper. The consequence to each is a lowering of the resistance to injurious mechanical or chemical influences, with resulting inflammatory disturbance of the circulation, stasis, and more or less extensive necroses.

The causes of necrosis being, as we have just seen, so very diverse, you will not expect the condition of necrotic parts to be always the same. How could a part that has mortified from desiccation or scalding resemble one killed by the action of caustic potash or one that has perished from laceration or from complete deprival of blood? Add to this the manifold and important differences in the various tissues of the animal body as regards consistence, watery contents, colour, vascularity—their entire structure and chemical composition,

in short—and it will at once be evident *that local necrosis may present itself under the greatest variety of aspects.* Still we can distinguish a number of forms in which necrosis is wont to appear, and some of these have obtained special names. These forms are, it is true, as I shall at once confess, in part conditioned by secondary changes in the dead tissues, and should not, properly speaking, be discussed, except in connection with the subsequent history of the necrosis.

In the first place, a necrotic part may completely *retain its normal appearance.* This is observed in very hard and compact structures, as bones, cartilages, hyaloid membrane, whose habitus is so little altered by death that, for example, a necrotic piece of bone is recognised by the very smoothness of its surface, and thus distinguished from the carious, and therefore roughened, bone in the vicinity.

The second form is that in which the altered appearance of the part is determined by the loss of water, *desiccation.* Where the loss is slight, and the dead tissues undergo no further change, the appearances produced may have the strongest resemblance to those of the first category. Examples of this are presented by the so-called *calf mummies, i. e.* embryos of the cow which, owing to torsion of the gravid uterus, die and remain lying in the uterine cavity; occasionally too by the dead embryos of extra-uterine pregnancy, in which part of the water of the tissues is removed slowly by resorption from without, for in these cases the fœtus is connected with the maternal organism solely by means of the investing capsular sac. In such cases, all the tissues, muscles, nerves, connective tissues, &c., may retain for many years, not merely to the naked eye, but also under the microscope, their nearly normal characters, modified only by a moderate degree of drying.* In encapsuled dead parasites, *e. g.* trichini and cysticerci, an analogous state of things may not rarely be observed. Much greater changes occur when, on the other hand, the tissue-fluids of a necrotic part can easily and rapidly evaporate. For the part then shrivels till it becomes a tough, dry, dark brown or black mass, and may in appearance vividly remind one of an Egyptian mummy. This form of necrosis, which is termed *dry gangrene* or *mum-*

* Cf. Forster, 'Ztschr. f. Biolog.,' xiii, p. 299.

mification, is a physiological process when occurring in the remnant of the umbilical cord of the new-born; pathologically we have often an opportunity of observing its most typical form in lower extremities attacked by senile or by spontaneous gangrene. The appearance of mummification in these cases always depends on the antecedent loss of the epidermis, usually by the formation of bullæ. How vastly evaporation is facilitated by removal of the epidermis may be most simply demonstrated on a rabbit's ear, in which severe inflammation has been set up by a temporary ischæmia or by plunging it into hot water or the like. Every spot from which you strip off the epidermis (over a vesicle, for example) mummifies infallibly, while the rest of the ear either heals or develops the moist variety of gangrene. In this way is to be explained, also, the *scabbing* of all wounds and external ulcers when evaporation is not artificially checked. For a scab is nothing but the dried secretion of the wound plus the uppermost layers of tissue that have undergone necrosis and drying from loss of water. If the protective covering is lost, the ordinary amount of evaporation is sufficient to produce a necrotic scab, but with the epidermis intact a very much greater degree of heat is necessary. The slough in gangrene also partly owes its peculiarity to the loss of water.

As regards altered consistence, there is a pretty close connection between the variety of necrosis just discussed and a third form, although the two are in their essential nature utterly different. The characteristic feature of this third form is an alteration of aggregate condition, which may best be denominated *coagulation* or *clotting.* And this name is appropriate not only because the condition of the necrotic tissues has the greatest resemblance to *firm coagulated albumen,* but because the process concerned is, as a matter of fact, indistinguishable in all essentials from the process of coagulation as known elsewhere. Solutions of albumen may be coagulated by heat; they may also solidify through precipitation of the dissolved albuminates by heavier salts of the metals or other chemical reagents; but in physiology the most important of all is the so-called *spontaneous* clotting, in which the liquid albuminous bodies assume a solid aggregate condition by uniting together under the influence of a ferment

that has somehow been set free. The most thoroughly studied example of this form is the coagulation of the blood. Now the agencies which are influential in bringing about a necrosis with coagulation are quite analogous to the foregoing. Here too the coagulation may sometimes be determined by heat or by the precipitation of the albuminates, as occurs in many cases of scalding and corrosion. Much more commonly, however, the coagulation-necrosis is spontaneous, or caused by the internal conditions of the organism. Just as the coagulation of the blood is attributable to the formation of fibrin by the combination of certain substances, set free during the destruction and disintegration of the colourless blood-corpuscles, with the fibrinogen of the liquor sanguinis, so it happens here too that certain substances contained in the tissue-cells become free by diffusion or other means, after the death of the latter, and join with the lymph that bathes the cells to form a body of the nature of fibrin. The chemical processes characteristic of coagulation-necrosis are still very far from being elucidated, even to the extent of placing it on a par in this respect with the coagulation of the blood. Still it will be simplest to suppose that, in accordance with the views of Alex. Schmidt, a fibrin ferment and a kind of fibrino-plastic substance is supplied by the tissue-cells, while the lymph contributes the fibrinogen. Weigert,* to whose researches we owe the greater part of our knowledge on this subject, takes a similar view of the process; and it is at any rate certain that a necrosis with coagulation occurs only when (1) the dead part contains an abundance of coagulable material, and (2) is everywhere intimately bathed in lymph. Both conditions are equally necessary; if there be an absence of coagulable albuminous bodies, as in the brain, the lymph bathing the dead tissue may be ever so plentiful, yet, instead of gaining in cohesion, the part goes on losing consistence till it becomes fluid. On the other hand, it is enough to point to the behaviour post mortem of tissues rich in protoplasm to show how indispensable is the lymph to the production of coagulation-necrosis. The latter

* Weigert, 'Ueber pockenähnliche Gebilde in parenchymatösen Organen und deren Beziehungen zu Bacteriencolonien,' Breslau, 1875, und "Aufsätze über Diphtherie," 'Virch. A.,' lxx, p. 461, lxxii, p. 218, lxxix, p. 87.

must be carefully distinguished from the change called rigor mortis occurring in tissues which are contractile and abound in protoplasm; in rigor mortis the product is not only much less firm and without the histological peculiarities of coagulation-necrosis, soon to be discussed, but is a mere temporary solid state which again passes off after a short time. Accordingly these two conditions must be fulfilled if true coagulation is to occur in the dead parts. Since, however, it is at least possible, and indeed very probable, that all structures in the interior of the body, even when they have through some cause become necrotic, will still be bathed by the lymph —wandering cells constantly penetrate them—we must agree with Weigert in his belief *that parts of the body rich in protoplasm which die in the living organism will as a rule undergo coagulation-necrosis,* in so far at least as coagulation is not prevented by the influence of some third factor. That there are agents calculated to check coagulation you know from the history of inflammatory exudations; for we were able to show (p. 327) that pus-poison not only prevents the formation of fibrin in the exudation, but is even capable of dissolving formed fibrin. In this respect a still more important part is played in the history of necrosis by the *putrefactive ferment;* where putrefaction sets in coagulation is at an end, and what has already solidified softens and becomes fluid.

Nevertheless, the chances of coagulation in necrotic parts are so very numerous that we shall not err in regarding the coagulative as the most usual of all the forms in which necrosis manifests itself in the body. For to this category belong in the first place by far the greater number of necroses conditioned by circulatory disturbance in tissues abounding in protoplasm. Here must be placed the entire group of the so-called *infarcts,* whether complicated by hæmorrhages, as are the hæmoptoic pulmonary infarcts, or associated with small and circumscribed, or no bleedings, as is usual in the kidney and spleen. The peculiar opaque, almost clay-coloured appearance of the latter is due solely to the coagulation. Still more typical perhaps is the habitus of the small infarcts of the *heart-muscle* from embolism or thrombosis of single branches of the coronary. To the same category belong the

so-called *caseous* patches, which are met with so very commonly in the middle of the most different tumours—especially if these be rich in cells—and whose cause is also to be sought most probably in the inadequate supply of the part, involved in the degeneration, with circulating blood. To a similar circumstance must be attributed, according to Weigert, the origin of the *typhoid* necroses, in which he found a thrombosis of the small arteries produced by disease of their walls. But let the cause of the necrosis taking place in the typhoid infiltration of the intestinal follicles or mesenteric glands be what it may, the necrosis itself is coagulative. Moreover, *tubercular* and *scrofulous caseation* is nothing but a coagulation-necrosis, though it is still uncertain whether obstruction of the vessels, or rather the non-vascularity of the new formation, determines the necrosis, or whether the latter is called forth by the direct action of the tubercular virus. The latter alternative is the more deserving of consideration, since, as already noticed, nothing is more indubitable than the necrotic influence of certain of the schizomycetes. Almost every colony of micrococci, after remaining for about a day or longer in one spot, is surrounded by a border of necrotic tissue, which one fails to see only when violent inflammation has set in, and pus-corpuscles have penetrated as far as the colony ; that the necrosis is here accompanied by coagulation we learn from the microscopical appearances. The part played by coagulation-necrosis in *diphtheritic* and *croupous* inflammations will soon be discussed at length.

In a fourth form of necrosis the consistence of the dead tissues is diminished; the part softens and liquefies—a process which is termed *colliquation* or *inodorous gangrene.* The most indispensable factor in the softening is the prevention of a loss of water by rendering evaporation impossible and by checking absorption by the blood-vessels and lymphatics of the neighbourhood. If the watery contents of the necrotic part continue unaltered, and still more if it be increased by lymph or exudation flowing into it from without, this is enough to give rise, in tissues containing no coagulable protoplasm, to a softening which is often rapid, or even to complete liquefaction. The classical instance of this is *encephalomalacia* after occlusion or sclerosis of arteries (p. 558). A similar soften-

ing occurs in coagulable tissues also; indeed it chiefly selects necrotic parts that have previously coagulated, *e. g.* the interior of caseous lymphatic glands, lobes of the lung affected with caseous pneumonia, as well as the cheesy portions of tumours. That thrombi also soften is well known to you. It is not easy to explain how the softening is produced here. In the liquefaction of tubercular products and the puriform softening of thrombi infective influences may certainly have a share, yet such can hardly be assumed for the liquefying caseous masses in tumours and the simple softening of thrombi. It may be that the lymph, not meeting with any more coagulable material as it constantly penetrates from without, destroys the cohesion of the parts already coagulated; or it is possible that these portions were from the first less firmly clotted, so that the in-flowing lymph would most easily accumulate here. Finally, it is not impossible that leucocytes entering the necrotic tissue from its periphery may have a share in producing the liquefaction.

There is a further variety of necrosis—differing from all the preceding forms—in which the dead parts *undergo putrefaction,* and which is termed *moist gangrene, gangræna humida, sphacelus,* or simply *gangrene.* It is characterised by the well-known processes of decomposition, called collectively putrefaction; and these processes, I need hardly tell you, are invariably set up by organised ferments, the *bacteria of putrefaction,* which in the vast majority of cases arrive in the dead part from without. The other known conditions must, it is evident, be fulfilled before the bacteria can display their activity; above all there must be a sufficiency of moisture in the dead part. Hence it is that moist gangrene selects by preference the interior of the body, and attacks the extremities when the epidermis is intact; thus it involves the deeper parts of a leg which has mummified superficially and is therefore protected against further loss of water. The maintenance of a warm temperature is also, of course, favorable to the production of true gangrene. The process is not really distinguishable in any essential particular from putrefaction such as takes place in every dead body. As in colliquation, a *softening* and *liquefaction* set in, and usually at the same time a *discoloration,* which is due to the diffusion

and further decomposition of the colouring matter of the blood. Bluish-red stains resembling livores arise, and then the colour inclines to green and black. Owing to the formation at this stage of various ammoniacal and fatty acid compounds, the gangrenous part acquires a peculiar, partly stale, partly empyreumatic, intensely penetrating *odour*. The epidermis is often raised into blisters containing a diffusely stained bluish-red fluid. Occasionally there are developed in the gangrenous soft parts gas-bubbles, consisting of ammonia, sulphuretted hydrogen, and volatile fatty acids; we then speak of *gangræna emphysematosa*. The final result is disintegration of the tissues into ragged, greasy, discoloured particles, accompanied as a rule by the separation of leucin- and tyrosin-crystals, needles of fat, and crystals of triple phosphate. The conditions and organs in which moist gangrene appears will be clear from a few simple considerations, and I have, moreover, indicated them just now. The external parts of the body, *e.g.* the extremities, and those internal organs which are always easily accessible to the germ-containing air, like the lungs, and like the internal genitals of the female, are the true seats of election. If gangræna humida affects other organs it is owing to infection with gangrenous ichor by direct extension—of which more anon—or to the transport of putrid thrombi from a gangrenous focus. Only extremely seldom does the pathological anatomist meet with a gangrenous patch whose origin is not thus explainable; so rarely indeed that the absence of moist gangrene in all kinds of internal necrosis may with some justification be utilized in proof of the non-existence of putrefactive bacteria in the juices and tissues of the physiological organism. That the first and second forms of necrosis practically exclude the development of gangræna humida, follows naturally from what has just been stated.

Finally, *mould-production* is usually mentioned as a last variety of necrosis. Yet this is not so much a special variety as a process which may sometimes complicate any of the other forms except moist gangrene, for the well-known incompatibility of the bacteria of putrefaction with the hyphomycetæ applies of course to the human organism also. It is not at all surprising that the ordinary moulds should, just

as on any other organic nutrient substratum, grow on dead parts of the body to which air is admitted, when the proper spores are, so to speak, sowed upon them. A copious formation of moulds is indeed not uncommon in the most superficial epithelial layers of the mouth and pharynx, where these, though dead, have for some reason failed to be removed; and no better substratum is presented here than by other tissues of the animal body. The entrance of the hyphomycetæ into the living tissues, *e. g.* from the cavity of the mouth, whence access is extremely easy, is prevented, in so far as the want of free oxygen does not act as a check, chiefly by the energetic metabolism of the tissues to which the parasites would quickly succumb. If indeed the conclusion arrived at by Grawitz (p. 498) from his experiments be correct, a still better safeguard against the penetration and further development of the hyphomycetæ is provided by the alkaline reaction of the tissues and juices of our body. For moulds which he had habituated by gradual cultivation to an alkaline substratum, instead of the ordinary acid one, were seen, as I already informed you, to flourish in a most vigorous, and at the same time destructive, manner in the organism. But whether this be a genuinely cultivated or a merely accidental variety, such as in a similar manner was happened on by Grohé and Leber, it is none the less certain that the common hyphomycetæ do not thrive in the living tissues of the animal body. It would indeed be strange that a mould-formation so seldom occurs in necrotic parts as is actually the case, were it not that a simple explanation is found in the antagonism, already referred to, between the hyphomycetæ and the bacteria of putrefaction. Only such dead parts as are freely exposed to the atmosphere can become mouldy; but these parts are for the same reason specially open to invasion by the bacteria of putrefaction; *they do not become mouldy, because they putrefy.* Such being the case, the comparatively rare instances where collections of moulds have been met with in diseased patches in the lungs* are interesting rather as curiosities. Moreover the patches themselves were in part markedly and purely necrotic, and had in part more

* For the literature of pneumonomycosis *vide* Fürbringer, 'Virch. A.,' lxvi, p. 330; cf. also Rother, (Neue) 'Charité Annalen,' iv, p. 272.

the characters of necrosive inflammation. They were invariably *odourless,* and the absence of smell is sufficient to distinguish them in all cases from the foci of pulmonary gangrene.

All the events embraced by this category, which come under observation in pathology, may be ranged under one or other of the forms of necrosis just described; especially if the peculiarities of the individual tissues and localities be duly considered. So it is with embryos dying *in utero.* The variety which is appropriately termed *fœtus papyraceus,* is evidently nothing but the result of a necrosis with drying, mummification, and develops only on the early disappearance of the liquor amnii by resorption. The commoner variety, however, which is usually formed when the fœtus perishes in the later months of gestation, *the macerated fœtus,* is due simply to necrosis with liquefaction, colliquation; and is produced by the action of the abundant liquor amnii upon the dead fœtus. That a fœtus already covered by a normal skin, and possessed of a complete skeleton, which is everywhere cartilaginous at least, cannot be totally transformed into a soft pulp will surprise no one. The soft parts proper, *e. g.* the brain, really disintegrate so far; the liver also becomes quite pulpy, and the bones of the skull separate from one another. The peculiar reddish-brown colour of these macerated fœtuses, reminding one of dirty potters' clay, is due solely to the saturation of all the tissues by free and altered blood-colouring matter. The complete absence of coagulation in the dead fœtus is not surprising, if we remember that the composition of the liquor amnii is altogether different from that of lymph, and that the entire process is in no respect to be identified with the irrigation of a dead mass by constantly renewed supplies of lymph: it resembles nothing so much as the maceration of an anatomical preparation in standing water, putrefaction of course excluded.

As to the microscopic appearances of the dead parts, I need only amplify a little on what has been said when speaking of the various forms of necrosis. For in some cases, like dry gangrene, the microscopic appearances require no elucidation; in others, like putrefaction and mould-formation, the striking feature is the presence of putrefactive bacteria

or of hyphomycetæ, a description of which you can also dispense with. For only a very moderate degree of interest can at bottom be excited by the morphological processes which lead to disintegration of the tissues into shapeless, crumbling, ragged particles. On the contrary, that form of necrosis which is accompanied by coagulative rigidity of the tissues will well repay somewhat closer investigation. True, a mere hasty survey would make it appear that microscopic examination of tissues in coagulation-necrosis would be attended by little profit. Just as a muscle-fibre in rigor mortis or a dead epithelial cell of the liver or kidney is not essentially distinguishable in optical properties from the living, differing at most in having a somewhat duller, more lustreless hue, so the simple observation of a microscopic section of a tissue in a state of coagulation-necrosis at first reveals so little of a striking or abnormal character that it seems in fact as if the diagnosis might be more certainly made by the naked eye than by the microscope. There is hardly a post-mortem appearance which catches the eye more than an embolic non-hæmorrhagic *infarct of the kidney*, with its tawny, yellowish-white, dry section, in such evident contrast to the red neighbouring parts. A microscopical section, provided the infarct is still recent, shows, on the other hand, the urinary tubules with their different kinds of epithelium in apparently the most beautiful order. The same may be said of cardiac infarcts where the muscle-fibres display the same regular cross-striping as do those of the healthy musculature, however prominent the difference of colour of the two parts to the unaided eye. Ligature a branch of the hepatic artery distributed to a single lobe of the rabbit's liver, and the contrast after about twenty-four hours between the remaining juicy, dark brown liver and the dull and fawn-coloured, almost dry lobe is significant in the highest degree. Compare, on the other hand, microscopical sections of the two parts, after having first washed them in salt-solution to remove the blood, and so like are they that they might be mistaken the one for the other. Nevertheless, this apparent optical identity must not be rated too high. Not only does the agent by which coagulation is brought about modify, in certain circumstances, the appearance of the cells, which *e.g.* are made yellow by nitric acid

and caused to swell strongly by potash or ammonia; but even in the absence of such complications the cells dying in a coagulated condition invariably display an abnormal behaviour to all kinds of colouring reagents—if not from the first, at any rate eventually, because the dead cells sooner or later undergo further alterations. Of these none is more remarkable than the *disappearance of the nuclei;* this very soon takes place in the great majority of cases, usually commencing a few hours after death with indistinctness of the nuclear contour, and being completed mostly within twenty-four hours. Neither in infarcts—so-called *fibrin-wedges*—nor in croupous and diphtheritic pseudo-membranes; neither in the foci surrounding colonies of micrococci, nor in the various kinds of caseous patches is it possible, any more than in white thrombi, to bring the old cell-nuclei into view, either by acetic acid, carmine, hæmatoxyline, Bismarck brown, or other nuclear stain. The nuclei are also wanting in many of the acini of the dead hepatic lobe, if the animals have survived the operation a somewhat long time.

Disappearance of the nuclei, however, is not the sole alteration experienced by dead cells. *Diminution* and *shrinking of their nuclei,* as well as *vacuolar degeneration,* are also not infrequently observed. It is possible too that their disintegration into smaller fragments, particles, such as are often seen in the immediate neighbourhood of eschars and the like, should in these cases be referred to the necrosis, although we shall also meet with them in other conditions. A *swelling* and *granulation* are sometimes noticed in the protoplasm of the dead cells, while certainly the most common change is the gradual loss of their sharp contours, an actual blending and *obliteration of the cell-boundaries,* which is the harbinger of the complete destruction and disappearance of the cells. In addition the dead cellular material occasionally acquires a peculiar *glittering* appearance. All these alterations are very essentially influenced by the necrosive agent, as before remarked; and at any rate no general rule can be laid down with regard to them. Indeed, I should not have dwelt so long on this subject, were it not that I wished again to bring home to you the fact that we have here to do only and solely with *necrotic* processes, and that

therefore nothing could well be more erroneous than to look upon the changes in the form and appearance of the tissue-cells as the expression of some vital processes or other.

The forms of necrosis, the naked-eye and microscopic characters of which have just been portrayed, are, you will observe, so different the one from the other that we cannot reasonably expect to find any general *diagnostic mark* of gangrene. Evidently, common to and characteristic of necrosis generally is *cessation of all the functions* of a part; dead muscles can no longer contract, a dead gland cannot secrete, a dead nerve cannot conduct, and so on. Hence a part that has died is quite *devoid of sensibility;* it produces no heat, and in so far as it receives none from the vicinity, is *cool*—a sign which is very marked in gangrenous fingers or toes, and in superficial parts generally. In all other respects the greatest diversity prevails according to the form of the gangrene. I may remind you that a mummified foot is considerably harder, while the parts of the brain affected with encephalomalacia are very much softer, than normal. A leg attacked by moist gangrene acquires the consistence of œdematous parts, so that we are justified in speaking of the *false œdema* of sphacelus; and if the gangrene be emphysematous we get on palpation a feeling of peculiar crepitation. Similarly with the *colour:* a part that has perished through want of blood and coagulated may have a faint grey or even white appearance, while it is wont in moist gangrene to assume a bluish-red hue which later becomes greenish and blackish—changes due to diffusion of the colouring matter of the blood. The occurrence of further alterations depends essentially on whether the necrotic mass comes or does not come into contact with colouring matters; for the dead, unlike the living tissues, become stained by imbibition of any coloured solutions bathing them. Hence it is that the sloughs of the small and large intestine in typhoid are usually yellowish brown, but black if perchloride of iron has been administered. This fact is so certainly established that it even affords a reagent to determine the setting in of necrosis in superficial parts. Bile dropped into the eye of a rabbit does not impart the slightest tinge to the living cornea,

whether healthy or inflamed; while every necrotic focus, *e.g.* the dull grey speck with which neuro-paralytic ophthalmia commences, is stained a greenish yellow in its whole extent and depth.*

What is the *subsequent course* of a necrosis? What becomes of the dead part, and what influence has the entire process on the rest of the organism? The limitation of the necrosis from first to last, or the contrary, is a factor of great importance in determining its course; in the former case we speak of *circumscribed,* in the latter of *diffuse gangrene.* Whether it be limited or not depends chiefly on the causes at work on each occasion; understanding by causes, not merely the immediate but also the remote, and in a sense *predisposing* ones, *i.e.* the circulation, functional capacity of the tissues—in short, the constitution of the individual. It may be said generally *that all necroses brought about by extinction of the circulation, or by direct traumatic disorganisation of the tissue-elements, or by abnormal temperatures, in an otherwise healthy individual, are wont to be and to continue circumscribed.* Wherever the ischæmia or the capillary stasis extends, there is arrest of the metabolism of such tissue-elements as depend on the vessels in question for their supply; in the neighbouring tissues the condition of the circulation is a very different one, and there is accordingly no ground for the development of necrosis there. True, in chemical, thermal, or other traumatic action on a part, it must be borne in mind that, as pointed out more than once, the vicinity of the spot directly affected by the trauma will more or less be drawn into sympathy with it; and, as a matter of fact, it is usual for a zone of tissue in direct proximity to the original erosion- or gangrene-slough or contusion to mortify later on. Yet this is nothing but a slight enlargement of the boundaries of the traumatic action; and even if we include the most unfavorable case possible, that in which secondary thrombosis and stasis occur in the vicinity, there would be added to the necrosed territory only a very small portion of tissue. It is quite otherwise with those varieties of necrosis *in which the defective constitution of the individual or of parts of the body plays an essential part,* such as senile gangrene, decubitus, the gangrenous processes

* Senftleben, 'Virch. A.,' lxv, p. 69.

in diabetes. Since a slight noxa is here sufficient to utterly destroy the metabolism of the tissues concerned, it is not to be wondered at that a necrosis established anywhere in itself constitutes a fresh noxa capable of causing the death of adjacent parts. Thus we see decubital gangrene invading extensively, and sometimes very rapidly, the hypostatically congested regions, and senile gangrene creeping from the toes along the foot and further and further up the leg, as far as the severe sclerosis of the small arteries, and with it the resistances opposed to the blood-stream extends. A still greater tendency to progression, if possible, is displayed by necrosis of infective origin. This character is partly to be laid at the door of the form just discussed, diffuse gangrene; for not uncommonly the first thing to appear around the primary infective gangrenous patch is an inflammation which, constituting as it does an important circulatory disturbance, itself establishes a predisposition to, and, influenced by the neighbouring gangrenous patch, terminates in, necrosis. But the intermediary inflammation is by no means necessary. At least, in the most pernicious cases, where an extensive necrosis develops very quickly on the poisonous agent gaining entrance to the tissues, the gangrene sometimes becomes rapidly aggressive; so that in a short time one portion after another of tissues till then healthy becomes involved in it. It is precisely in these really terrible cases that we shall be least likely to err if we ascribe a great, if not the greatest, part of the pernicious effects to the concurrent presence of *bacteria*. This assumption, at any rate, throws light on the eminently progressive character of the process, and also explains how, as a rule, only such primary infective gangrenous foci as have *a certain extension, i. e.* in which there is a great number of bacteria, are endowed with this capacity for progression. It is also clear without further explanation that the disposition to become diffuse will be most marked in moist gangrene, especially if it develops very rapidly. In the form of false red œdema—gangrenous bullæ being developed in various places and a penetrating, stinking odour given off by the affected parts—the moist gangrene creeps from the calf over the whole leg, involving the knee or even the thigh, *till,* if the patient survives so long, *it sooner or later becomes limited,*

and thus the diffuse terminates in a circumscribed gangrene, but only after very extensive loss. The final limitation, or, to employ the terminus technicus, *demarcation*, is very naturally explainable in one category of diffuse gangrene, for, agreeably to its character, the latter does not spread further than the predisposing circulatory disturbance extends. In the remaining cases we can but refer to the resistance offered by the normal metabolism and to the gradually diminishing intensity of the poison of mortification.

But whether the necrosis be throughout, or only subsequently, circumscribed, there is developed on its borders, in the immediate vicinity of the gangrene, an *inflammation*. Cases in which inflammation fails to set in are indeed the rare exceptions; but it may occasionally be absent in thin cutaneous sloughs, beneath which the epidermis is regenerated so perfectly and with such comparative rapidity that the eschar is completely isolated from its substratum, and falls off. True, this happens only when further decomposition of the slough is averted. And herein we perceive at the same time an indication of how it happens that the dead part is capable of exciting inflammation. But having regard to our many discussions on the nature of inflammation, it will not be necessary to deal minutely with this circumstance; more especially as we have already considered necrosis in its character of one of the most frequent causes of inflammation. On that occasion we were also able to lay stress on the fact that the intensity of the inflammation around the dead part is subject to the greatest variations. Its intensity is determined, for one thing, by the extent of the necrosis, and further by the resisting power of the vessels in the tissues abutting upon the gangrene. Where the resistance of the vessels is very slight, the inflammation, as we have seen, becomes necrosive; and this, we are now in a position to add, is very specially influenced *by the form of the necrosis*. Everything turns out much more favorably in circumscribed necroses of small or moderate dimensions which, situated in the interior of an organ, are remote from surfaces to which air or different fluids have access. For the inflammation around the dead part then remains slight and runs a chronic course, or at most is liable to occasional temporary exacerbations. The

events occurring in such a case are well known to you, and, comparatively innocent in themselves, here lead even to very desirable results. *The necrotic parts are first invaded by colourless blood-corpuscles, and afterwards traversed by newly-formed blood-vessels*; and as the former take up the particles of the dead mass, while the latter bring about the direct absorption of the débris, the dimensions of the necrosis will be gradually reduced. Its last vestige finally disappears, and what then remains is a *vascular connective-tissue cicatrix*. You have already, in the organisation of thrombi, met with a process which, as you will doubtless remember, was identical with this one even in its minute details; and indeed there is no reason why we should not regard a thrombus as a quantity of blood dying by coagulation, and its vascularisation and organisation as the effects of the reactive inflammation of the vessel walls. But even if we disregard this analogy, the same course of events may be observed in many cases which we are more accustomed to place amongst the necroses; *e. g.* in *infarcts of the kidney and spleen*, where it is the rule even for cicatrisation to occur. The isolated pus-corpuscles so often seen in the fibrin-wedges, or in the midst of the necrotic zone surrounding a colony of bacteria, are simply migrated cells, in which the nuclei may be brought out most beautifully by Bismarck brown, &c. But nowhere can the co-operation of the pus-corpuscles in the removal of the dead part, by taking up the products of its disintegration, be more clearly demonstrated than in *foci of cerebral softening*. For the much-discussed and highly characteristic *compound inflammatory corpuscles* of yellow softening, whether small or large, are nothing but lymph-corpuscles which have taken up the débris of the white substance of Schwann, and converted it into finer and coarser granules.

But the inflammation does not always terminate so favorably, even when it remains a productive one. When absorption of the dead tissue fails to be effected, by reason either of its bulk or of some quality rendering the process difficult, the productive inflammation leads to the formation of a *fibrous, vascular capsule*, by which the dead part is henceforward isolated from the remainder of the organism. This almost always happens around dead parasites; and it is not

uncommon for a lithopædion to become enveloped by a firm connective-tissue capsule. The really typical example of this, however, is presented by the capsules surrounding pieces of necrotic bone; these, being the product of a formative periostitis, are not fibrous but bony; they are, as you know, here called "cases" (*Laden*), while the portion of dead bone is termed a *sequestrum*. As you will notice from the instances given, we have here to deal chiefly with necroses associated with drying or complicated by calcification—of which more presently—or with the death of tissues rich in lime salts, and in the highest degree difficult of absorption. The dead masses may then remain for an unlimited period without the occurrence of any further change, and if they become encapsuled in the manner described, can still prove troublesome enough, and give rise, for example, to considerable local inconvenience, though to the organism as a whole they are rendered innocuous.

Hence it is in general better that the inflammation should take this course than that it should go on to *suppuration*. I need hardly tell you when suppuration sets in; for you will remember that we referred to profound decomposition of the dead parts as the cause which stamps traumatic inflammation with a more pernicious character. On this depends the occurrence of purulent inflammation in the cases now in question. When the necrotic part has still further decomposed under the influence of organisms that have entered it, and above all, when it *putrefies*, a purulent inflammation is developed with absolute certainty on its borders. It is mostly only a narrow zone that suppurates; just as in other kinds of reactive inflammation around necroses there is usually involved no more than a small portion of the neighbouring tissues. But as regards hyperæmia and exudation the course of the purulent inflammation is precisely the same here as elsewhere; as the result, a layer of liquid pus is formed on the boundaries of the gangrene, which is in this way actually encircled by a *demarcation-trench* filled with purulent matter. Once this has occurred, the necrotic part is much more thoroughly cut off from all connection with the organism than would be the case were a capsule interposed; it is—and herein lies the significance of this event—

completely *separated, dissected out.* What subsequently happens is determined chiefly by the circumstance that in the great majority of such cases the dead part borders more or less on the free surface of the body or of some internal cavity, such as the intestinal, genital, or respiratory tract. For in this way it is possible for the necrotic tissue to be cast off and removed from its original seat; the consequence being *a loss of substance, with a purulent inflammation at its base, i. e.* a true sore, *an ulcer.* This is the characteristic feature of all ulcers, however extreme the differences they present in respect of size, constitution, and course. The portrayal of these differences in detail, as well as their explanation, must be left to special pathological anatomy and to surgery; we are obliged to confine ourselves to establishing the broad outlines common to them all. In the great majority of instances, moreover, there is not the least difficulty in explaining the behaviour of a particular ulcer from the individual peculiarities of the case. The first determining factor therein is the *etiology* of the necrosis. For on it depends not merely the seat and area or depth of the ulcer, but in a great measure too its special habitus and the character of its base and edges; as is the case in *tubercular, syphilitic,* or *cancerous* sores, so clearly distinguished by the presence of cheesy, gelatinous, or marrow-like masses in their immediate vicinity. In the next place, the *form* of the causative necrosis demands our careful attention. It explains how, *e. g.* in dry necrosis or in necrosis with coagulation, the sphacelus is usually cast off at once, while in other cases the dead part gradually exfoliates in very small, often imperceptible, particles. In the latter instance the ulcer goes on increasing for a time till all the necrotic tissue is removed, in the former it instantly attains its full dimensions. The severity of the reactive inflammation and suppuration is also considerably influenced by the form of the necrosis. Then, too, in dealing with this factor of inflammation the general constitution of the patient as well as the peculiar structure of the part in which the ulcer is situated must be specially taken into account. According to the intensity of the reactive inflammation, we distinguish the *atonic* or *indolent* ulcers from the *erethical* or *inflammatory.*

The distinction into *œdematous, hæmorrhagic,* and *fungous* is made in reference to the characters of the base and edges, or to the variety of inflammatory reaction and the constitution of the inflammatory granulations. In no form of ulceration is the influence of locality so manifest as in *ulcus simplex ventriculi,* the base of which is always clean because the pus produced is at once exposed to the action of the gastric juice. The fundamental principle of ulceration, however, is nowise altered by a single example of this kind : *as there is no ulcer without antecedent necrosis, so it is,* in all circumstances, *the reactive demarcating suppuration that leads to the shedding of the necrotic tissues and thereby to the formation of the ulcer.*

In now inquiring into the further history of ulcers and their importance for the organism, it would certainly be absurd to judge wholesale of things so unequal in dignity. None of you will suppose that it is immaterial to a person whether an ulcer be a cancerous, a syphilitic, or simply a cutaneous one following a burn; and no one will anticipate a similar course for these ulcerations. Nevertheless, they all agree in one respect—that which at present chiefly, interests us—namely, that the ulceration is the means of *ridding the organism of necrotic tissues which are certainly worthless, and may even prove dangerous to it.* This is so at least when the ulcer is situated on the skin, or on a mucous membrane connected with the exterior by an open passage. When the dead part is got rid of completely, there remains a suppurating surface which, if the ulcer be uncomplicated by the presence *e. g.* of tubercular or cancerous nodules, heals like any other granulating wound. The healing is effected by the process with which you are already well acquainted, *i. e. the combination of regeneration with cicatrisation by means of productive inflammation.* This is the final fate of most traumatic necroses of the skin, and of many diphtheritic, syphilitic, typhoid, and other necroses of the digestive tract, the genitals, the urinary passages, the bronchi, and the lungs ; the only witness to whose presence is afterwards the radiating, sunken, contracted cicatrices, distinguished in pathological anatomy as "cicatrices with defect." For the existence of a defect is characteristic of a cicatrix resulting from necrosis, provided, at

least, the necrosis has not been too insignificant; and it must of necessity be so, because, as you know, the regenerative capacity of the various tissues is but limited.

Nevertheless, the *dissection* or separation of the dead part, which we learned a moment ago is a favorable termination to necrosis, may in certain circumstances prove highly obnoxious. When the slough borders on the surface of a serous cavity its separation will necessarily be difficult, and will, as a rule, result in purulent inflammation of the serous membrane. This is the origin of the purulent pleuritis occurring after dissection of peripheral infarcts of the lung, or associated with peripherally situated patches of pulmonary gangrene; in a similar way arises the fatal peritonitis following dissected infarcts of the spleen, or typhoid necrosis of a mesenteric gland, where the necrosis implicates the serous membranes; thus originate, lastly, the purulent pachy- and lepto-meningitis from necrosis and caries of the petrous portion of the temporal, discharging internally.

Thus, while necrosis is not uncommonly fatal by reason of the secondary, or, if you will, tertiary inflammation, there is also another modus in which an unfavorable termination may occur—one well known to you from preceding discussions. For you remember that amongst the causes of true *hæmorrhage per rhexin* gangrene was one; and that the bleeding is caused by the implication by erosion of vessels which had not previously undergone thrombosis. Its most striking instance is the fatal hæmorrhage by *diabrosis* from the a. lienalis or one of its larger branches, in consequence of simple gastric ulcer, while many of the bleedings from foul uterine cancers, though less violent, must still be classed under this head.

In conclusion we must not omit to mention that necrosis may prove pernicious to the organism, not merely as the result of local, so to say, accidental conditions, but can jeopardise life in quite another way, namely, by *direct poisoning with infective materials.* In which form of necrosis this will be observed almost goes without saying; it is the exclusive privilege of *moist gangrene.* I have already told you of the occasional occurrence of gangrenous embolism leading to the formation of secondary gangrenous patches, true *gangrenous metastases,* as the result of genuine gangrenous thrombosis.

of veins in the immediate vicinity of the primary focus. Still such cases are very uncommon, and therefore in practice incomparably less important than is the entrance from the gangrenous patch of a *dissolved exquisitely putrid poison into the fluids* of the body. The liquid saturating the part in a state of moist gangrene, the so-called *gangrenous ichor,* contains a poison of this kind, whose activity is intense; and so long as the gangrene remains uncircumscribed by demarcative inflammation there is nothing to oppose the passage of the dissolved poison into the lymphatics, or into such of the vessels as are free from thrombi. The result is profound constitutional disturbance, with severe irregular pyrexia: more or less violent derangements of the digestive organs, as vomiting and profuse, it may be bloody, diarrhœa, great prostration; and a frequent, but small, easily compressible pulse—a set of symptoms which usually gets the name of *putrid intoxication,* and for which the terms *septicæmia* and *ichorrhæmia* are also employed. That the poison to which septicæmia is due is not an organised one, that the *gangrene-* or *putrid-fever* is not to be attributed to the entrance of bacteria of putrefaction into the circulating blood, has by no one been more decisively or more accurately demonstrated than by Panum.* The putrid poison, such as is contained in every specimen of putrescent broth, blood, or the like, when introduced into the circulation of a horse, dog, or cat, operates immediately, *without the intervention of any incubation stage, and in direct proportion to the dose injected,* or the size of the animal experimented upon. Moreover, the most energetic chemical treatment, prolonged boiling, or shaking with alcohol, failed in Panum's hands to destroy its activity. And if, as against this, several later writers† have succeeded in weakening the activity of the poison by means of similar manipulations, such as repeated filtration, it must not be lost sight of that many chemical substances in solution, *e. g.* the

* Panum, 'Virch. A.,' xxv, p. 441, lx, p. 301; the second essay contains the chief references to the literature.

† Kehrer, 'Arch. f. exp. Path.,' ii, p. 33; Bergmann, 'D. putride Gift u. d. putride Intoxication,' Abth. i, Heft 1, Dorpat, 1868; 'Deutsch. Zeitschr. f. chir.,' i, p. 373; Burdon-Sanderson, 'Brit. Med. Journ.,' 1877, 22nd Dec. and following; 'Practitioner,' 1877, cix, p. 19; translated in 'Wien. med. Jahrb.,' 1877, p. 396.

pancreatic and salivary ferments, are inclined to precipitate on any fine corpuscular particles, and there in a measure to condense, without it being necessary that the latter should be living beings. Nor is it impossible that the repeated filtration, especially through earthenware, may occasion certain chemical changes in the filtered substances which are calculated to impair their physiological activity. The view of Panum, according to which the putrid poison is a substance soluble in water, and analogous probably to the vegetable alkaloids, seems to me extremely plausible after all; and the failure heretofore of the many attempts* to isolate it may simply be owing to its not being a single body, but, as Panum supposes, composed of several poisonous materials. True, since this poison forms during putrefaction, it is indebted for its origin to the bacteria of putrefaction; but this is no reason for calling putrid fever a bacterial disease. As though to demonstrate *ad oculos* the incorrectness of such a view, colonies of bacteria are often found in the myocardium, the kidneys, or the liver of persons who have been killed by gangrene of the lung or of a leg; but these colonies are surrounded by the usual grey zone, which, though a putrid gangrenous focus is present in the body, shows nothing but the appearances of simple coagulation-necrosis. That the colonies have obtained access to the juices of the body from the gangrenous patch is, to say the least, highly probable; and yet no one would dream of making these isolated colonies responsible for the general intoxication of the body. Still such complications give one a clear idea of the difficulties to be contended with in judging of the cases in which this disease comes in question, as well as in investigating it experimentally. Where putrid gangrene has obtained a footing, bacteria must be present; and it is equally certain that every putrescent liquid swarms with them. It is therefore unquestionable that bacteria may be present coincidentally with the development of the morbid phenomena appearing in such circumstances; and that they actually are present will seem to you very likely, on reflecting that *bacterium termo*

* Bergmann und Schmiedeberg, 'Med. Ctbl.,' 1868, p. 497; A. Schmidt, 'Untersuchungen über d. Sepsis,' I.-D., Dorpat, 1869; *vide* also note *, p. 393.

is not the only form contained in putrefying tissues and fluids, but that many others, to which the animal body does not oppose an equal resistance, are also found in them. But is one for this reason justified in referring every pathological symptom occurring in a human being affected with putrid gangrene, or in an animal after the injection of decomposing fluids, to the schizomycetes? It was with the view of coming to a certain conclusion on this point that Panum instituted the above-mentioned experiments, whose cogency in my opinion has not been shaken by the analogous experiments of subsequent writers. But the end which Panum sought to secure by the direct removal of the organisms from his putrid fluids has been attempted in a different manner by Mikulicz,* who before injection mixed the putrid fluid with a quantity of glycerine sufficient to kill the bacteria. The picture presented by the animals so treated differed, the disease being much milder than when living bacteria, capable of multiplying, were also introduced. Still less open to objection seem to me the experiments of Koch,† who succeeded in distinguishing perfectly the effects of putrid intoxication from those of the infection with simultaneous introduction of organisms simply by reducing the dose of putrid fluid to a minimum. As might be anticipated, the course of the parasitic infective disease was only very slightly influenced by diminishing the quantity of virus; while whatever effects were due to the dissolved poison, *i. e.* the intoxication, altogether failed to appear, as soon as the amount of the poison fell below a certain limit. Both must therefore be sharply distinguished from one another; and though it cannot be denied that a moist gangrenous focus may become the cause of a parasitic infection of the body, not merely in the immediate vicinity of the gangrene but in more remote regions also, still the specific gangrenous or putrid fever does not depend on these transported organisms, but is the effect of a *soluble* poison produced at the seat of gangrene. The term *putrid intoxication* is for this reason very appropriate; and it were to be desired that the name *septicæmia*, or per-

* Mikulicz, 'Arch. f. klin. Chir.,' xxii, p. 253.

† Koch, 'Untersuchungen über d. Aetiologie d. Wundinfectionskrankheiten,' Leipzig, 1878.

haps better *ichorrhæmia*, could also be applied solely, in the sense originally given it by Virchow, to denote poisoning by dissolved, unorganised materials. Meanwhile, our terminology is in this respect far from fully fixed ; and when surgeons nowadays speak of sepsis and septicæmia, the majority at any rate do not intend to express anything but the fact that infective noxæ have asserted their influence in a person suffering from a wound or some other surgical affection. How very far from true it is that all writers have the same disease in mind when employing the term septicæmia is most clearly shown in the use made of it by Davaine.* He applies it to a disease artificially produced by him, which he claims is characterised *by an increasing virulency of the blood of the diseased animals.* When, for instance, he could kill a rabbit by the subcutaneous injection of ten drops of putrescent dog's blood, half a drop from the heart's blood of the dead rabbit sufficed to kill another ; while if blood from the latter was used the one hundredth part of a drop proved fatal ; and similarly, with each subsequent generation, always less, till finally incredibly small quantities of blood from the dead body proved deleterious. I expressly emphasize—*from the dead body ;* for that taken from the living animal showed itself completely innocuous. But, on the other hand, this increasing potency has nothing to say to progressive putrefaction ; for Davaine convinced himself that putrefaction, on the contrary, disturbs the activity of the septically infected blood. Were these facts, and more especially the conclusion drawn from them by Davaine, indisputable, we should have here a most remarkable affection, and one deserving to be distinguished by a special name. But we may pass over the fact that amongst the writers† who have repeated Davaine's experiments, some only have recorded the same success, while the results of others‡ have differed so greatly that the French pathologist himself would hardly recognise in them that con-

* Davaine, 'Bull. de l'acad. méd. de Paris,' 1872, Nos. 31—38 ; 'Union méd.,' 1872.

† Bouley, ibid. ; Vulpian, 'Gaz. hebdom. de méd.,' 1872, No. 51 ; cf. also Burdon Sanderson, 'Trans. Path. Soc.,' xxiii, p. 303.

‡ Dreyer, 'Arch. f. exp. Path.,' ii, p. 149.

firmation of his experiments which they claimed to afford. For we are raised above the necessity for all such considerations, since Koch* has proved, in his objective critique of Davaine's experiments, that the assumed augmentation of virulency does not really occur, and that Davaine made use of an infective poison which in the earlier generations was already capable of displaying the same intense activity that was only discovered by him to exist in the later ones.

Our discussion of necrosis would be essentially incomplete, did we fail to notice more particularly an affection which till now has received only passing mention, namely, so-called *diphtheria*.† Moreover, the diphtheritic processes occupy a peculiar position of their own, because in them necrotic and inflammatory changes are inseparably bound up the one with the other; so much so that their theoretical and practical distinction, possible in the forms of necrosis already discussed, is here impossible. The very name most generally employed, "*diphtheritic inflammation*" or "*diphtheritis*," points to such an intimate connection. True, the term diphtheritis is used by writers in very different senses. By it some understand the disease which is also known and dreaded under the name of "malignant angina." Others, when speaking of diphtheritis, nowadays think exclusively of the etiological factor, viz. a disease produced by the action of bacteria. Others

* Koch, 'Untersuchungen über d. Aetiologie d. Wundinfectionskrankheiten,' Leipsig, 1878.

† The description of diphtheria is based essentially on the investigations of Weigert; cf. also his article "Inflammation" in Eulenburg's 'Realencyclopäd.' In addition, see Bretonneau, 'Des inflammations spéciales du tissu muqueux et au particulier de la diphtérite,' Paris, 1826, addition supplémentaire, 1827; 'Arch. général.' 1855; Virchow, his 'A.,' i, p. 252, Hdb. i, p. 292; 'Deutsch. Klinik,' 1865, No. 2; Buhl, 'Stzgsb. d. bayr. Acad.,' 1863, p. 59; 'Zeitschr. f. Biol.,' iii, p. 341; Wagner, 'A. d. Hlk.,' vii, p. 481, viii, p. 449; 'Rindfleisch, 'Path. Gewebslehre,' 3 Aufl., p. 311; Cornil et Ranvier, 'Man. d'hist. path.,' 1869, p. 90; Klebs, 'A. f. exp. Path.,' iv, p. 221; Boldyrew, 'A. f. Anat. u. Phys.,' 1872, p. 75; Steudener, 'Virch. A.,' liv, p. 500; Oertel, 'Deutsch. A. f. klin. Mèd.,' viii, p. 242, xiv, p. 202; in Ziemssen's 'Handb.,' ii, p. 1; Trendelenburg, 'Arch. f. klin. Chir,' x, p. 720; Hueter, 'Med. Ctbl.,' 1868, p. 531; Nassiloff, 'Virch. A.,' l, p. 550; Ebert, 'Zur Kenntniss d. bacteritischen Mycosen,' Leipzig, 1872; 'Med. Ctbl.,' 1873, pp. 113, 291.

again, in their investigations into the affection, take up an *anatomical* standpoint. For us, who are dealing with the diphtheritic process in connection with local necrosis, the last-mentioned or anatomical conception is the most natural one.

We speak of a diphtheritic inflammation of a mucous membrane, *when the latter is covered by a more or less thick, yellowish- or greyish-white, tough, and tolerably dense, elastic membrane*, which, according to the cause and stage of the process, either forms an uninterrupted coating over a large area, or appears as disseminated islands or *plaques*, of smaller or larger size, that may subsequently coalesce and form a continuous pellicle. When the membrane, thus constituted, easily admits of detachment from the mucosa, we speak of "*croup*;" but of "*diphtheria*" proper if it must be torn away with a certain amount of force. On examining microscopically such a diphtheritic or croupous pseudo-membrane, it at once becomes apparent that the unquestionable resemblance to a fibrinous exudation, as observed by the naked eye, is fully borne out by its finer structure. For the great bulk of what is seen consists of a granular fibrillated material, the fibrils, as it is easy to understand, chiefly catching the eye. Some of these run parallel with the mucous membrane, and some are interwoven like a net; they are of very unequal thickness, being either comparatively fine with a faint lustre —common in croupous pseudo-membranes—or thick, trabecular, and tolerably brilliant—a more frequent appearance in diphtheritic membranes. In the granular material occupying the interstices of the fibrillar network are contained a variable number of pus-corpuscles, as well as other elements, which also vary and are some of them hard to be explained. Of these I must first mention the *epithelial cells*, though they, it is true, are never found unaltered in the pseudo-membranes. Rather they are either entirely absent throughout the whole extent of the membrane or have become transformed into irregular flakes, *which never contain nuclei;* in some such instances these flakes are in part scattered throughout the interior of the mass or may even lie on its surface, and in part coalesce to form larger aggregates. Again, the pseudo-membranes contain roundish bodies, which in shape and size remind one of pus-corpuscles, but are *without evident nuclei.*

As already remarked, the thickness of the membrane is very variable; sometimes it does not much exceed that of the epithelial layer of the affected mucosa, but it is often many times thicker. Its free surface may, of course, according to the locality, form a resting place for all kinds of foreign bodies, and the under surface towards the mucous membrane is therefore much more important. The character of this surface allows of our distinguishing two different, we may perhaps say, *fundamentally* different forms. In one *the under boundary of the epithelium is also the lower limit of the membrane;* it is so almost without exception in the trachea and larynx, as far as the basal membrane between epithelium and mucosa reaches; generally so in the pharynx, but more rarely the case in the intestine and uterus. Or *the pseudo-membrane extends more or less deeply into the mucous tissue proper,* so that its lower boundary passes right through the middle of the latter. In this variety, which, occurring rarely in the pharynx, is quite common in the intestine, uterus, and conjunctiva, the uppermost layers of mucous membrane are of course involved in the pseudo-membrane. They then appear under the microscope like tissues that have *perished by coagulation-necrosis;* the cellular portions seem as a rule to have no nuclei, the interstices of the tissues to be infiltrated by a compact granular material, from which pus-corpuscles are never absent. The difference just now emphasised is apparently so important that one cannot reasonably condemn those writers who are disposed to use it as a differential criterion between croup and diphtheria; according to them, when the pseudo-membrane lies *on* the mucosa it is *croupous,* when *in* it, *diphtheritic.* This distinction is strictly true only of *pure* diphtheria; for the rest, it must be borne in mind that what they call a croupous membrane does not lie upon the intact mucosa but invariably on the *stroma previously stripped of its epithelium;* and, again, that combinations of croup and diphtheria, or if you prefer it, *mixed forms,* are some of the most common occurrences. In these, while the diphtheritic pseudo-membrane passes more or less deeply down into the tissues of the mucosa, it also spreads out over the free surface of the epithelium, and thus in great part lies upon, not in it. If we compare these *microscopic* categories of croup and diphtheria

with the *macroscopic,* we sometimes find them both coinciding, for example in croup of the larynx and trachea; yet this is by no means constant. For the ease with which the pellicle may be detached, being the differential mark of macroscopic croup, is connected in certain organs with the presence of a firm basal membrane; where this is absent, as in the pharynx and intestine, the intimacy of the connection between membrane and mucosa may be very unequal. It is naturally a close connection when the membrane extends into the tissue of the mucosa; where, on the contrary, it ceases at the surface of the stroma, the amount of adhesion appears to be essentially *proportional to the thickness of the fibrinous trabeculæ.* Hence it follows that, in organs unprovided with a well-developed basal membrane, microscopic and macroscopic diphtheria are identical in cases where the specific process involves the mucous stroma. On the other hand, many cases in which the process stops at the lower limit of the epithelium, and which must all microscopically be denominated croup, belong to the domain of macroscopic diphtheria, as, for example, the great majority of such pharyngeal affections. The microscopic notion of croup is, you observe, more comprehensive than the macroscopic; all that in naked-eye anatomy is called croup is also croup under the microscope, but some cases which the microscopist regards as croup make the impression, on rough anatomical examination, of diphtheria. The contrary is, of course, true of diphtheritis, which is found on microscopic examination to embrace only a part of the cases which apparently belonged to it when examined by the naked eye. With a view to prevent misunderstanding, it might perhaps be best, following Weigert's example, to apply to the cases of this latter category, *i. e.* those which impress one as being diphtheritic, although the membrane does not exceed the lower boundary of the epithelium, the term *pseudo-diphtheria,* and to formulate the entire classification based on the microscopical appearances in the following manner. There is (1) *pure croup,* characterised by a fibrinous pseudo-membrane *lying upon* the tissue proper of the mucosa, and presenting itself macroscopically as croup or as pseudo-diphtheria; (2) *pure diphtheria,* also characterised by a fibrinous pseudo-membrane, but one passing more

or less deeply down into the tissues of the mucosa, and sending no extension over the epithelium; and (3) *a mixed form* consisting of croup and diphtheria combined—also called *diphtheritic croup*—in which both occur, the infiltration of the mucous tissue as well as the extension over the free surface; the latter two forms appear as diphtheria to the naked eye. Let us, in conclusion, briefly consider the mucous membrane underneath the pellicle. It is always more or less intensely *inflamed;* the vessels are hyperæmic and the capillaries contain a very great amount of colourless corpuscles; a quantity of leucocytes, more or less large, is also met with in the mucous tissue between the vessels (more numerous in diphtheria than in croup), and punctiform hæmorrhages are quite common in diphtheria.

Now, how is the entire process to be interpreted? As already noted, we have to do with *an inseparable conjunction of necrosis and inflammation.* That the croupous membrane projecting free over the surface of the mucosa originates in an exudation from the mucosa, or rather from its vessels, need not of course be specially proved; the resemblance in morphological and chemical characters between the mass and a fibrinous exudation from a serous membrane is complete even in its minutest details. Now you know that in common inflammation of a mucous membrane, in catarrh, no matter how violent, a fibrinous exudation is never produced. Hence it follows that some additional peculiarity must be present in the cases now engaging our attention. This is the *death of the epithelium.* The living epithelium manifestly prevents the coagulation of the inflammatory exudation, which must first force its way through the epithelial layers before it can reach the free surface; but if, on the contrary, the cells have mortified there is no longer any obstacle to the occurrence of coagulation. *Without the death of the epithelium* (in its entirety and inclusive of the lowermost stratum) *croup cannot occur.* If a thin layer of epithelium is found under a croupous pseudo-membrane in the trachea or pharynx, it is, I still hold in spite of Posner's* opposition, invariably in the peripheral zone of the affected part that this happens, either because the exudation stretches fungus-like for a short

* Posner, 'Virch. A.,' lxxix, p. 311.

distance over the adjacent intact epithelium, or because a regenerated epithelium has already begun to insinuate itself beneath the pseudo-membrane. It is immaterial how—in what form and by what agency—the epithelium is killed, and whether its débris remains or is cast off and removed. Croupous pseudo-membranes in man, as a rule, show no vestige of epithelium; in the tracheal croup, which may be produced in a dog or a rabbit by inhalations of hot steam, the epithelium also separates *in toto*, and has completely disappeared before a characteristic croup-membrane is formed; in many other cases of artificial croup the flakes previously described represent the remnants of the epithelium. None of these points are of any importance in the entire process, because *the epithelium per se has nothing to do with the coagulation, the production of fibrin.* Rather, the fibrin is formed in these cases also by its usual generators, *i. e.* it arises through the mutual influence of colourless, disintegrated blood-corpuscles and the fibrinogen of the inflammatory transudation. I need hardly say that the transuded fluid as well as the colourless corpuscles are derived from the blood-vessels of the mucosa, which are stimulated to yield this inflammatory transudation by the same agency which caused the death of the epithelium. It is possible even that the mucous tissue proper is specially predisposed to abundant exudation of this kind; perhaps because, owing to its density, it does not admit of such an accumulation of colourless blood-corpuscles in its meshes as is quite practicable, for example, in the subcutaneous and submucous cellular tissue, and in the laxer connective tissues generally. It would then have a certain analogy with the serous membranes and the tissue of the alveolar septa of the lung, inflammations of which are also distinguished, as you know, by the production of an exquisitely fibrinous exudation.

Not only is the croupous pseudo-membrane which projects above the surface of the mucosa in greater part a fibrinous exudation, but *the exudation also participates* very essentially *in the formation of the diphtheritic material deposited in the mucosa.* The form-giving element, if I may called it so, is the *necrosis of the tissues,* without which a diphtheritic infiltration could never occur. Wherever the diphtheritic mass in-

filtrates the tissues the constituent elements of the latter have all of them died; but the specific, peculiar *stiffness* and *solidity* is acquired only through the intimate admixture of the inflammatory product which exudes into the dead part from the subjacent still living layer of mucous membrane. By means of this thorough saturation alone does the dead part acquire the qualities characteristic of fibrinous *coagulation;* and hence we may look upon the diphtheritic pseudo-membrane as falling into the domain of coagulation-necrosis. Nothing more clearly shows how large a share of the diphtheritic material is contributed by the inflammatory product than the presence of those roundish, non-nucleated bodies, previously described; these are often met with in large numbers within the diphtheritic pellicle, and are simply coagulated colourless blood-corpuscles. But in cases of pure diphtheria also the epithelium has completely disappeared from the area involved in the diphtheritic process, in most instances simply because the cause producing necrosis of the mucous tissue at the same time kills the epithelium clothing it. Yet even if it were not so, if the necrosis of the mucosa were somehow conditioned from within, it would be inconceivable that the vitality of the epithelial layer should be maintained after the mucosa underneath it had perished. We may dispense with an examination in detail of the mixed forms, inasmuch as there is in them a mere combination of the peculiarities of croup and diphtheria. Their origin is all the more intelligible, as we have in the great majority of cases to deal with a primary croup with which a diphtheria only afterwards becomes associated.

From the interpretation of the diphtheritic pseudo-membrane just given you, the further history of the diphtheritis may be readily deduced. Since life is extinct throughout the entire area of the pseudo-membrane, its separation is a mere question of time. Separation is effected without difficulty when the membrane is loosely superimposed on the part, when the croup of rough anatomy is concerned. But in order that a firmly adherent diphtheritic pseudo-membrane may be shed, it is necessary that its connection with the mucosa be first destroyed; and this is effected, as in all necroses, by means of a demarcative inflammation. Inflam-

mation already exists, indeed, in the mucosa underneath the membrane, and a transformation of fibrinous exudation into suppuration is the only thing needed for the dissection and immediate removal of the diphtheritic mass. The condition of the mucosa after the pseudo-membrane is cast off chiefly depends of course on the depth to which the latter had extended. Under no circumstances is the epithelium present on a mucosa from which such a membrane has just been shed. The appearance of integrity which the mucous membrane of the trachea, for example, presents, on inspection by the naked eye, is therefore not real; the membrane may seem as smooth as ever, and yet microscopic examination discovers the epithelium wanting. But only immediately after removal of the pellicle; for *regeneration of the epithelium* very soon commences, and when completed the membrane is perfectly restored, without any cicatrix or other vestige to indicate recovery from so severe a disease. In the cases of malignant angina also, which to the naked eye appear diphtheritic, but are not so on microscopic examination, it is unusual for cicatrices to remain after healing, because the process has ceased at the junction of epithelium and mucosa. Where, on the contrary, a genuine microscopic diphtheria is present, as often happens in the intestines, healing without cicatrisation is impossible, since the mucous tissue proper, with its many specific apparatus, glands, follicles, &c., is not endowed with so considerable a capacity for regeneration as is surface epithelium.

Upon what I have told you of the nature of the diphtheritic process, we may easily base our answer to the question of the etiology of diphtheria. It may be produced by any agent which causes necrosis of at least the epithelium of a mucous membrane, and at the same time acts as a strong exciter of inflammation in the mucosa. Both are manifestly necessary; without the death of the epithelium there would be no pseudo-membrane, while without inflammation of the mucosa the formation of a pellicle would, if possible, be still more out of the question, since destruction of the epithelium would simply be followed by its regeneration. But you will please take the words "at the same time" *cum grano salis;* any influence which at first merely kills the epithelium, and

then by its permanency prevents regeneration, thereby becomes an exciter of inflammation for the naked mucosa. Impressed by this and other similiar considerations, you will easily understand how it happens that the application of any *corrosive* to the tracheal mucous membrane of a rabbit or dog, ammonia, nitric acid, acetic acid, alcohol, &c., produces the most beautiful and typical croup. Precisely the same effect is caused, as already stated, by hot steam which the animal inhales through a tracheal cannula. Analogous results are observed in human pathology, *e. g.* in the mouth, pharynx, œsophagus, and stomach after poisoning with sulphuric or nitric acid. The diphtheria which is often met with in the cæcum after the internal administration of calomel may be referred simply to corrosion by the sublimate, and the diphtheria of the intestines in Bright's disease to a similar action of the ammonium carbonate. No less intelligible are the diphtheritic processes originating in *mechanical mortification* from direct compression of the epithelium, or of the uppermost layer of the mucosa. To this category belong the diphtheria of the large intestine due to pressure by hard fæces in sporadic dysentery or in front of strictures; the diphtheria of the vermiform process from pressure of a fæcal calculus; that of the mucous membrane of the gall-bladder from gall-stones; of the mucosa of the pelvis of the kidney and urinary bladder from renal and vesical calculi, &c. In all these cases the area, depth, and intensity of the process depend on the nature and strength of the agent, and on certain easily observed peculiarities of the locality. Thus the distribution of sporadic diphtheria, or dysentery, in the large intestine is simply explained by the existence of tæniæ longitudinales and crescentric folds in this portion of the alimentary canal, these being chiefly exposed to the pressure of arrested fæcal masses; and similarly the linear diphtheria of the œsophagus by the fact that the acid flows over the summits of its longitudinal folds. But whether the epithelium shall alone be involved, or portions of the mucous membrane be simultaneously or subsequently implicated in the process, depends in all cases on the severity of the corrosive action or of the mechanical pressure. In mere death of the epithelium, croup or pseudo-diphtheria is developed; in instantaneous mortifi-

cation of the superficial layers of the mucosa, pure diphtheria; and in subsequent extension of the process to the mucous tissue proper, the mixed form, or diphtheritic croup.

In addition to these forms of diphtheria, whose genesis as a rule presents no difficulty, there is still a number of diphtheritic processes, and these the most severe of all, in which any attempt at a mechanical or chemical explanation is bound to fail, and for which we must have recourse rather to an *infective agent.* We meet them (1) on the soft palate and pharynx as *malignant angina,* which seldom extends to the mouth and nasal cavity, but much more frequently spreads into the larynx and windpipe with the bronchi, and may, moreover, appear primarily in the localities last named; (2) in the large intestine, as *epidemic dysentery;* (3) in the female genitals, almost exclusively of lying-in women, as *puerperal diphtheria;* (4) in the eye, as *diphtheria of the conjunctiva.* All these varieties possess, in the first place, one anatomical feature in common; they are all distinguished by the disease commencing in the form of small whitish or yellowish-white specks, *plaques,* which gradually undergo a more or less rapid increase, and then usually coalesce *to form continuous membranes,* a circumstance perfectly harmonising with the capacity for, and *tendency to, further extension,* eminently characteristic of these diphtherias. But much greater importance attaches to their agreement in certain etiological respects. These diphtherias appear to be all exquisitely *contagious.* For pharyngeal and laryngeal croup, diphtheria of the conjunctiva, as well as the puerperal variety, this character is established beyond all doubt; but it appears very probable that it is a feature of true dysentery also, more especially when we consider that this affection, like the three others, is exclusively and markedly epidemic in its manifestation. There are, indeed, some remarkable facts going to show that the poison of pharyngeal croup, when conveyed to the eye, can produce diphtheria of the conjunctiva, and this would make for a much closer relationship between these diseases than we meanwhile assumed for them. A third and last factor impressing a special character on these diphtherias is the invariable *implication of the entire organism.* The forms of diphtheria previously discussed may indeed prove severe, and

in certain circumstances even fatal affections, but they are always *local* in character, while epidemic pharyngeal croup and puerperal diphtheria are constantly accompanied by pyrexia and general lassitude, prostration of energy, and the like. With the contagious diphtherias, secondary affections of internal organs are very frequently associated, as *e. g.* swelling of the spleen and lymphatic glands, enteritis, nephritis, none of which are ever seen in the purely local form; while the much-discussed and still enigmatical *paralyses* or pareses of some muscle-groups, especially of accommodation, are apparently the monopoly of the contagious malady.

The peculiarities to which prominence has just been given will be sufficient, on the one hand, to vindicate the right of these diphtherias to a special place of their own, and, on the other, to justify us in ranking them with the *infective diseases.* If you call to mind what I formerly told you of the infective virus, you will assuredly hold it to be *a priori* extremely probable that an organised poison is also present in these diphtherias, and that we have here to deal with the *action of bacteria.* As a matter of fact, the pathogenic influence of schizomycetes was very early called on for the explanation of infective croup of the pharynx and larynx; and the assumption of their agency has since been more thoroughly supported by actual facts than is the case with most other infective processes. The presence of single micrococci, or even of colonies, upon and in the pseudo-membrane would, indeed, for obvious reasons prove nothing; but really good observers have repeatedly detected colonies in the mucosa underneath the croup-membrane, and chiefly, it would appear, in the lymphatics: moreover, small collections of bacteria are in these cases often found in the myocardium, the liver, the kidneys, and other organs. In view of the positive results recorded in the literature, no weight should be attached to the fact that it is not always possible to discover the colonies. For to say nothing of the possibility that cases of pharyngeal croup occurring sporadically—in which no colonies could be discovered in this institute—should be kept distinct from the epidemic form, just as chlolera nostras from Asiatic cholera, we know too little of the detailed history of the bacterial infection in these cases to specify the conditions in which one

may expect, for example, to still find, or no longer to find, the colonies. For the same reason I am altogether unable to formulate a theory of the bacterial action. I wish only to direct attention to one circumstance—how excellently it harmonises with the hypothesis of bacterial action that infective diphtheria invariably begins in the form of *minute patches.* In direct contrast to a poison in solution and, say, circulating in the blood, the schizomycetes establish themselves strictly locally, not merely in a particular organ but in circumscribed portions of that organ; only subsequently involving in the diphtheritic process—most likely by their continued multiplication—larger and larger areas of the mucosa. The action of the poison produced by them must undoubtedly be pictured as in the main necrosive, but also as exciting inflammation in the mucous membrane; and it is most likely perhaps that in the majority of cases the infection takes place progressively from without inwards. But anyone who distinguishes between croup and diphtheria according to the microscopic criteria previously laid down, cannot logically recognise anything but differences of degree in infective croup and infective diphtheria. Even when the distinction between the two processes is drawn from their macroscopic features only, the matter is not essentially different. For in those mucous membranes where both occur, the adhesion of the pellicle depends, as you know, either on its reaching down into the mucous tissues, or on the existence in the false membrane of numerous, specially thick, fibrinous trabeculæ, closely connected with the surface of the mucosa—conditions which point simply to a greater intensity of the necrosis or of the inflammation.

The facts on which the view just enunciated is based—a view which discovers in *specific schizomycetes* the virus of infective diphtheria—at present refer chiefly, as I must not conceal from you, to diphtheria of the throat, and possibly to the puerperal affection as well; while the evidence in the cases of the large intestine and conjunctiva is very weak and insufficient. Similarly there is a dearth so far of appropriate observations on the diphtheritic affections so often setting in as sequelæ to the other infective diseases. I am not thinking so much of the diphtheria of the pharynx after scarlet fever

and smallpox, which is I believe beyond doubt closely related to primary angina or perhaps identical with it, as of the diphtheria following *typhus* and *cholera*. After both these diseases extensive diphtheritic ulcerations not only of the pharynx and œsophagus but also of the gall-bladder and vagina are sometimes developed; and widespread *diphtheria of the small intestine* often long retards recovery after an attack of cholera, and may even prove fatal to the patient. After it had been determined in the cholera epidemic of 1865 and 1866 that the epithelium of the small intestine is not shed, as was formerly supposed, the earlier explanation of the intestinal diphtheria broke down. To me at least it appears decidedly more judicious to regard this diphtheria not as being due to local causes, but rather as analogous to the diphtherias of the localities above-mentioned, and so to bring it into relation with the infective nature of the primary disease. True, the details of this connection are still hidden from us.

It is of special interest, finally, that infective diphtheria is capable of being conveyed to other tissues besides the mucous membranes. Thus, the *surface of a wound* may be attacked by it. In this way a very disagreeable accident sometimes occurs after the *operation of tracheotomy*. The most superficial layers of the wound-surface may become infiltrated with a firm, hard, yellowish-white mass, resembling the croup-membrane both microscopically and to the naked eye, the subsequent fate of which mass is identical with that of such membranes. But even where direct infection of contiguous parts does not occur, the surface of a wound or ulcer often becomes diphtheritic; and there is much in favour of the view that the so justly dreaded *hospital grangrene* is nothing but an infective diphtheria attacking the surface of wounds. True, when the nosocomial gangrene penetrates into the deeper parts and converts, as it so often does, the tissues of a stump into a pultaceous mass, or in a manner eats directly into them so as to give rise to deep crateriform ulcers, the disease cannot properly be termed infective diphtheria; we must speak of it as infective necrosis with colliquation. For to diphtheria the characteristic firm and hard pseudo-membrane which is formed by the intimate admixture of the inflammatory product with the dead tissue is essential. But since a mem-

brane can only be formed on and immediately beneath a surface, the naturally selected seats of diphtheria are the mucous membranes, the surfaces of wounds, and perhaps the valves of the heart. In the serous membranes the analogue of diphtheria would be a fibrinous inflammation by which at the same time the epithelium is killed—a very common complication indeed. On the other hand, there is no such thing as a diphtheria of the uninjured skin, since, owing to the structure of the epidermis, free exudation is here impossible. Moreover, when parenchymatous organs become infected with diphtheritic masses, the result is either a severe inflammation, leading ultimately to necrosis, or a simple necrosis with secondary purulent inflammation, such as was seen in the many recent attempts at inoculating the cornea. A *diphtheritic keratitis* or *croup of the cornea does not exist* in the sense in which this term is applied to conjunctivitis diphtheritica or to pharyngeal croup; an affection involving the establishment of a yellowish-white, elastic pseudo-membrane on the convex surface of the cornea, and accompanied by destruction of the anterior layer of epithelium, *cannot exist,* simply because by far the greatest portion of the cornea is extravascular and therefore incapable of producing a fibrinous exudation. Owing to this incapacity, the alteration in the cornea produced by inoculating the corneal tissue with diphtheritic material cannot be identified even with pure diphtheria, any more than could neuroparalytic keratitis after division of the trigeminus, in which the most typical necrosis with progressive purulent inflammation is also found. For from the anatomico-histological standpoint taken up by us, necrosis with secondary inflammation is not diphtheria; the other doctrine, which defines the disease according to its etiology, was discarded by us from the first. But in any case it would be judicious to restrict the term *diphtheria* or *diphtheritis* to genuine pseudo-membranous affections of the mucosa or the surfaces of wounds, and to give some special name to the necrotic-inflammatory patches of parenchymatous organs, depending on etiological factors similar to those of infective diphtheria of the mucosa. Moreover, the *identity* of the causes is not proved in all these cases; the contrary is true of some of them. Thus it is quite impossible that the

above-mentioned change in the cornea should be produced only by inoculation with *diphtheritic* masses; the same result is secured by the use of any putrid or other decomposing material.* In variola, moreover, not only is the specific skin-pock solely the effect of a central necrosis due to infective agency with secondary inflammation at the base and periphery of the pustule, but many of the internal organs very commonly contain foci, not always to be diagnosed with certainty by the naked eye, the central portion of which is constituted by dead tissues and the periphery by a zone of secondary inflammation. These foci, the seats of characteristic micrococci-colonies which cannot easily elude observation, are nowise distinguishable in optical or chemical properties from the oft-mentioned foci containing bacteria, which are so frequently met with in true diphtheria of the pharynx, also in moist gangrene, and no less commonly in some wounds and ulcers. But who would therefore suppose the virus of smallpox to be identical with that of diphtheria, or, still less likely, with that of grangræna humida, &c.? The very most that can be said appears to me to amount to this: the organised poisons of various infective diseases agree with the poison of pharyngeal diphtheria in giving rise to necrotic-inflammatory processes wherever they establish themselves. But if they are not even etiologically identical, the name diphtheria appears quite inapplicable to them. If, however, by this term it be desired to express that the process occurring in the skin and parenchymatous organs is in some degree analogous, or even related, to true diphtheria of mucous membranes—as there is unquestionable ground for believing—it might be advisable to make use of the expression "diphtheroid," as proposed by Weigert.†

* Leber, 'Med. Ctbl.,' 1873, p. 129; Stromeyer, 'A. f. Ophthalmol.,' xix, Abth. 2, p. 1, xxii, Abth. 2, p. 101; Frisch, 'Experimentelle Studien über d. Verbreitung d. Fäulnissorganismen in d. Geweben, &c.,' Erlangen, 1874.

† On the subject of this chapter consult further Virchow, 'Hdb.,' p. 278; C. O. Weber, 'Hdb.,' p. 548; Wagner, Billroth, &c.

CHAPTER II.

SIMPLE ATROPHY.

Object of the pathology of nutrition.—Causes of simple atrophy.—Passive atrophy from defective blood-supply.—Inanition.—Active atrophy of muscles, glands, bones.—Senile atrophy.—Physiological atrophy of particular organs.—Puerperal atrophy of the uterus.—Febrile atrophy.—Atrophy after use of iodine and lead.

Condition of atrophic parts.—Atrophy and aplasia.—Atrophic multiplication of nuclei.—Degree of atrophy.—Significance of muscular atrophy for the growth of bone.

Neurotic atrophy.—Cross and circumscribed atrophy.—Peripheral atrophic paralyses.—Spinal muscular atrophy.—Progressive atrophy and pseudo-hypertrophy of muscle.

A PART in which the vital metabolic processes are completely suspended dies, undergoes *necrosis*. This is unquestionably the greatest possible change which the nutrition of a portion of the body can sustain. But the pathology of nutrition is not merely concerned with extremes; it is equally if not still more interested in the lesser degrees of quantitative and qualitative disturbance of the physiological tissue-metabolism. In physiological conditions, the change of substance in the elements of the tissues is effected in such a manner that the material taking the place of the old is exactly the same in amount and composition—except of course during normal growth. The consequence is that normally all tissues and organs have a stable constitution. But we meet with a number of cases in which single organs or parts of organs, though unaltered in other respects, are *smaller* than they should normally be. In another set of

cases we find *a change in the chemical composition* of tissues and organs, *e. g.* a substitution of fat for albumen, lime in excessive quantities, or even the presence of substances not occurring in the physiological organism, such as *amyloid.* In a third set we are struck by the abnormally large size of organs or parts of organs, or by the presence of masses of tissue in situations where to normal anatomy they are unknown. In these circumstances we conclude, and correctly, that in the cases of the first series less is replaced than was consumed; that in the second, some special chemical process, differing from the normal ones, takes place in the tissue-elements; and that in the last, repair, restoration, exceeds waste. We may consequently expect that a scientific pathology of nutrition should explain all these deviations from the normal. True, a really satisfactory explanation can only be given by *chemistry,* because the nutritive disturbances just mentioned are collectively and individually the result of chemical processes. Even the most accurate knowledge of morphological details can never be more than a sort of guiding principle in formulating more precisely the actual problems awaiting solution. When, for example, we have acquired a minute acquaintance with calcification of the arteries—how the finest possible granules of lime first become visible in the arterial wall, how more and larger ones appear beside them, till finally hard and rough calcareous plates, over a centimetre in size, render the vessel wall uneven; or when by careful microscopic examination we have determined the situation and distribution of the fat occupying the epithelium of the convoluted or straight tubules, or the interstices of the kidney, in Bright's disease; we have in reality only cleared the way for the consideration of the proper problem of the pathology of nutrition. For if we wish thoroughly to understand the various nutritive disturbances of the tissues it is necessary to discover both their *determining causes* and the *intimate chemical processes* engaged in them. Only by physiological chemistry, you observe, can we acquire the power of foretelling in individual cases what influence a particular circulatory disturbance, a particular alteration in the composition of the blood, or a particular derangement of function, must exert on the constitution of the tissues and organs;

and the ultimate aim of the pathology of nutrition can be no other than this. How distant it now is from its goal will be but too manifest from the following discussion.

The form of nutritive disturbance which most readily admits of analysis is that in which an organ or part of an organ is simply *smaller* than normal, while in structure and chemical composition it remains unaltered, *i. e. quantitative* or *simple atrophy*. For there is not the slightest ground for assuming of these cases that the chemical metabolic processes in the tissue-cells occur in abnormal order, or are of an abnormal kind. On the contrary, it may be unhesitatingly affirmed that we have here to deal merely with a reduction of their energy, and with a diminution in the quantity of material worked up by the tissue-cells, the materials themselves being as before. But we stated the conditions of normal nutrition to be, 1, the regular supply of suitable material to the cells; 2, the capacity or excitation of the cells to take up the material, to assimilate, split it up, oxidise it, &c.; and 3, the maintenance of a normal temperature. Hence, we must logically expect that the nutrition of a part will be imperfect and less than normal, 1, *if suitable material be conveyed to it in insufficient quantities, and* 2, *if the tissue-cells fail to make use of an adequate amount of material;* the result is of course still more likely to ensue when both these factors coincide. As to the manner in which changes of bodily temperature influence the nutrition of the tissues, no opinion, so far as I see, can be given *a priori.*

To the first category belong all those *factors by which the entrance of arterial blood into the capillaries, or the flow through them, is impeded.* Such are all local anæmias, whether produced by an increase of internal resistance, as in sclerosis and parietal thrombosis, or by external causes, such as compression from the contraction of bands of connective tissue, from tumours, bandages, &c.; such are all anæmias depending on nervous influence, as well as all varieties of venous stagnation—provided only they are pronounced and persistent. The last point, the long duration of the circulatory disturbance, is an essential condition, if the nutrition of the part is to be affected by it; though, as I need hardly say at this stage of our inquiry, many tissues react to such disturbance

with more energy and quickness than do others. There is no dearth of illustrations in pathology that the circulatory derangements just mentioned, if they be not merely transitory in character, give rise to simple atrophy of the affected organs or parts of organs. Granular atrophy of the kidney and liver following interstitial nephritis and hepatitis; the furrows produced by tight lacing, the feet of Chinese, hydronephrotic atrophy of the kidney, the thinning of skin and muscle or even bone under the pressure of tumours, aneurysms, or varices; smooth atrophy of the kidneys from sclerosis of their small arteries, and, lastly, the dwarfing, non-development of an extremity, the afferent vessels of which are imperfectly formed, are all proofs as convincing as any that could be devised by experiment. Such an experiment was mentioned, however, on a former occasion, namely the extreme atrophy of the kidney which Buckwald and Litten secured by ligaturing the v. renalis in rabbits (p. 209).

All these examples concern single organs or parts of organs, because the circulatory disturbances on which the atrophies in question depend are local ones. It is not, of course, implied that the entire organism may not also react similarly to analogous noxæ. General circulatory disturbances, such *e.g.* as arise as the result of non-compensated cardiac lesions, are not of so much consequence here as is *defective composition of the blood.* The transudation from which the tissue-elements draw their materials is, you know, derived from the blood; and although a portion of it, increased by the products of the tissue-metabolism, re-enters the circulation by the lymphatics, the blood would speedily become impoverished in matters capable of transudation, did not the chyle constantly supply it with suitable materials. When, therefore, the chyle-stream proceeding from the intestines and emptying itself into the blood remains for a long period too small or too poor in organic and inorganic substances, this must react on the nutrition of the tissues. The result is most evidently seen where no nourishment is taken, in *inanition,* which, since Chossat, has been repeatedly made the subject of experiment* in dogs, pigeons, and other animals,

* Chossat, 'Récherch. expér. sur l'inanition,' Paris, 1843; Collard de Martigny, Majendie's 'Journ. de phys.,' viii, p. 152; Bidder und Schmidt,

and which has also come under observation in more or less marked form in persons afflicted with melancholia, who persistently refuse food, or in individuals with stricture of the œsophagus. In such cases the supply of oxygen to the tissues is not diminished, the oxidative processes do not at first suffer, and whatever easily oxidisable substances are present in the body, like fat and glycogen, are almost completely consumed. So much the worse prospect for the material which is offered to the cells by the transudation for the replacement of that which is being continually used up. It is true, certainly, that consumption now becomes gradually less, as is apparent from the uninterrupted fall in the excretion of urea in starving animals or men. Nevertheless, decomposition, waste, goes on everywhere as long as the individual lives; thus a bodily decrease must necessarily result, —a decrease which will be most marked in the early period of starvation, but becomes constantly less as inanition continues. This, however, is nothing but an *atrophy* in which all the organs and tissues must have their share. But by no means *equal* shares. Of the adipose tissue it has already been said that by far the greatest part of it disappears. The loss is next most marked in the spleen, testicles, liver, and muscles; while the bones, and above all the central nervous system, are very slightly affected. The causes of the extreme differences in the degree of inanition-atrophy are certainly complex, and we are not justified in arguing from them as to the extent of the metabolism of the various organs in a normal condition. That the blood will participate in the general atrophy is at once apparent; its amount is pretty accurately maintained in the well-known proportion to the total weight of the body (in dogs 7·7 per cent.), and its composition remains as before except for a certain degree of hydræmia. But the effect which is in these cases due to absence of food may, it is clear, be produced approximately when the *nourishment taken is not absorbed.* Instances of this are presented by large gastro-colic fistulæ and other

'Die Verdauungssäfte und der Stoffwechsel,' 1852, p. 328; Heidenhain, 'Arch. f. phys. Heilk.,' N. F., 1857, p. 507; Panum, 'Virch. A.,' xxiv, p. 241; Bischoff und Voit, 'D. Stoffumsatz im hungernden Thiere;' Voit, 'Zeitschr. f. Biol.,' ii, p. 307.

severe diseases of the digestive organs, and especially by the non-compensated stenosis and obliteration of the ductus thoracicus, previously referred to. How very slight the difference is between these cases and those of complete inanition is often demonstrated *ad oculos* in the frightful emaciation of patients suffering from cancer, or from phthisis, of the intestines.

In addition to the variety conditioned by a diminution in the supply of nutriment, and termed *passive* atrophy, there is another, *active*, form which plays a no less important part in pathology. This arises despite an adequate supply, or at any rate independently of it, either because the tissue-elements are incapable of effecting the necessary chemical changes, or because the stimulus thereto is wanting. Muscles not in use, *i. e.* which for a considerable period do not contract, glands which do not secrete, bones which no longer subserve the statical purposes of the organism, *atrophy.* It is quite immaterial whether the inactivity of the muscle be due to failure of innervation through central or peripheral causes or to absence of an object for contraction, as in ankylosis of joints or after removal of its insertion by amputation. Nor is it at all important whether the failure of a gland to secrete be caused by defective innervation or by occlusion of its excretory duct. I am, of course, far from denying that considerable weight must be attached in the latter case to the accumulation of secretion and resulting compression of the vessels in the gland; yet we are taught only too clearly by all the other examples that a great, if not the greatest, share in the atrophy is attributable to the abeyance of function. In such unnatural states nervous excitation to muscular contraction and to secretion is at an end. Why a permanently inactive muscle or gland atrophies becomes obvious enough on considering that regeneration, the repair of waste, is adjusted and brought to pass by the contraction and secretion. On ceasing to work, whatever would have resulted from their activity towards influencing the production of new elements is no longer effected. Add to this the circumstance that the active congestion of the arteries supplying them also ceases, and you will have no difficulty in understanding the falling-off in volume of the thigh muscles which occurs in ankylosis of the knee-joint, or the wasting to a thin

membrane of the intestine below a large fæcal fistula or so-called anus præternaturalis. Atrophy of bone is attended, if possible, by still more striking results. The gradual reduction in size of the bone of a stump, the wasting of the alveolar portions of toothless jaws, or of the rim of the acetabulum after an unreduced luxation of the femur, above all, the disappearance of bony callus after repair of a fracture, are most typical examples of true atrophy. Moreover, our knowledge of the metabolism of bone renders these atrophic processes perfectly intelligible. We know that by means of *giant-cells,* Kölliker's *osteoclasts,* osseous substance is constantly absorbed, and that new material is no less constantly deposited by the vessels of the periosteum or cartilage; we also know that these events are controlled by *statical conditions.* In a place where bone subserves no statical purpose there is no deposit; and what can be the result of continued resorption without deposition except the atrophy of the affected bone?

Although we have applied the term *active* to all the atrophies of the category just discussed, and with good reason, because their ultimate cause must be sought in deficient function, *inactivity,* of the organs or parts of organs, still it will not have escaped your notice that a faulty circulation *i. e.* a scanty supply of nutritive material, often co-operates in their production. Both these factors coincide in a still more marked manner in *senile atrophy.* Inquiring into the causes of this condition—which is well known to the laity, and for which the term senile marasmus is also employed—we find, certainly, that a determining influence is in the vast majority of cases exerted by tangible pathological factors. In one instance it is a disturbance of respiration, in another of digestion, in a third of the nervous system or of the renal function that forms the first link in the chain of processes, more or less morbid, the result of which collectively is senile marasmus. We shall also soon see how calcification and fatty degeneration often arise as complications. Nevertheless, an individual who had never passed through any actual illness would in old age most certainly become the subject of senile atrophy. It is in my opinion the constancy with which in aged people a more or less marked atrophy of *all* the organs

sets in, quite independently of the number or character of antecedent pathological processes, that clearly favours the view according to which the conditions determining the occurrence of senile atrophy are, so to speak, physiological. True, the conditions are only with difficulty discoverable, and their nature is certainly complex. A wear and tear, such as occurs in machinery, must evidently be confined to tissues whose metabolism is slight and whose permanency is consequently great; it was thus I explained the decrease of elasticity in the arteries of old people (p. 100). No such change can take place in the great majority of organs, simply because they are continually undergoing transformation and renewal, so that the individual elements composing the tissues and organs are in aged persons by no means old. The principal question appears to me to be whether, when the necessary material is supplied them, the faculty of self-renovation, *the reproductive power of the cells, is really unlimited.* All these matters are involved, indeed, in the deepest obscurity; and, as I should be the last to deny, nowhere in this domain have we a secure foundation to build upon. Yet if we fix our attention on the development of an organism, noticing how rapid is its growth at first and how this gradually becomes feebler, and attempt to understand the laws of its causation, we shall again and again find ourselves inclining to one and the same hypothesis. This is the existence in the component cells of the organism of an inherent reproductive capacity transmitted by inheritance, most active in early life, and as age advances losing energy little by little, till after a time it just suffices to maintain the size of the body or its parts, and at last fails even to do this. But we should then have discovered the principle at the root of senile atrophy, the further progress of which must in many ways be assisted by the gradual appearance in its train of functional disturbances, *e. g.* of digestion, circulation, blood-production, &c.

The correctness of this hypothesis is, I think, most strikingly borne out by the physiological atrophies. Single organs may normally undergo atrophic changes before old age sets in, many of them long before this. The pupillary membrane disappears during embryonic existence, and the thymus within the first year of extra-uterine life. Atrophy of the genitals,

though a much later event, occurs, more especially in women, when the rest of the body is at the height of its strength and functional power. These atrophies unquestionably arise so soon as the organs undergoing them can be of no further service to the body, and have thus become in a measure superfluous. But the recognition of this fact does not clear up the modus in which the organism initiates the "adaptive" atrophy; it throws no light on its proximate cause. To assume that the thymus atrophies because the other organs appropriate larger and larger quantities of blood during their growth, and thus indirectly impoverish the gland, is but to mask the real question at issue; for why the thymus fails to keep pace with the muscles, spleen, &c., in development is no more apparent than before. Our knowledge of facts is most nearly, if at all, adequate to explain such atrophy in the case of the premature senescence of the female genitals. To me it appears highly plausible to attribute this change to the consumption of all the ova. When all the follicles have ripened, menstrual congestion is definitively at an end, for there is, as is well known, no after-production of new ones. Possibly this circumstance is in itself explanation enough, but it may be that the ordinary intermenstrual circulation also becomes feebler. In any case we have here a clue to the diminution of the blood-supply, and hence to the atrophy of the genitals. But should not this explanation admit of application, *mutatis mutandis,* to the other physiological atrophies? If so, the implication is that the thymus becomes atrophic so soon as its elements lose their reproductive capacity. The function of the organ as well as its individual existence is dependent on the continued substitution of new cells for old ones. Hence the loss of reproductive capacity involves a gradual extinction of its hypothetical hæmapoietic function, no less than a termination to its growth; no apposition of new cells taking place, atrophy must inevitably result. In other words, the thymus grows old and feeble at a time when the rest of the organism is enjoying the full bloom of youth. If this be so we are clearly right in considering physiological atrophy with the *active* category.

The intimate connection between function and blood-supply, already noticed in the active atrophies just discussed,

is nowhere more apparent than in the process *of involution of the uterus after expulsion of the fœtus.* This process must undoubtedly be placed among the true atrophies, although fatty degeneration plays a part in it. Since separation of the placenta cannot be effected without hæmorrhage, delivery must always give rise to anæmia in the mother; and this, you are aware, may sometimes be extreme. The remainder of the blood will be appropriated by the various organs requiring it in the discharge of their functions; and the quantity of blood restored by regeneration will not be more than the work of the organs collectively demands. Once delivery has taken place, however, the uterus subserves no further end—none, at least, to meet which so large an organ as the gravid uterus is required. The result is not only a primary anæmia of the uterus immediately following delivery, but a persistence of this condition long after the muscular contraction has given place to relaxation. With the anæmia atrophy becomes associated—an atrophy so rapid and marked that the weight of the uterus is reduced within a fortnight from 1000 to 350 grams.

In addition to the passive, active, and mixed atrophies, there is further a *febrile* form, depending, it is claimed, on the third factor premised by us, namely, abnormal temperature. I do not deny, of course, that pyrexia is constantly attended by loss of weight, that a decrease of the constituents of the body takes place in it; yet the question at issue cannot be disposed of by simply establishing a connection between rise of temperature and atrophy. Where the temperature is raised from fever or other cause the decomposition of nitrogenous material will be abnormally great. But it has not been shown that all the remaining constituents of the cells participate to the same extent in the decomposition; and, indeed, you will shortly become acquainted with facts which seem even to make against the idea. Certainly, increased decomposition could lead to atrophy of the affected organs only when it failed to be compensated by increased repair. But fever patients, as everyone knows, take little nourishment, and digest and absorb still less; and so the principal share in febrile atrophy may be credited to the inanition.

It is much more difficult to understand certain atrophies

which arise after prolonged use of particular drugs, of which *iodine* and *lead* are the chief. Their peculiarity consists in the limitation of their action to completely isolated parts. When iodine is employed continuously for some time the thyroid atrophies; and the loss is most extreme when the organ has been previously greatly enlarged. A frequent feature in saturnine cachexia is atrophy of the extensors of the forearm. Why the atrophic effect of these poisons is thus localised still awaits a satisfactory explanation, although the subject has been repeatedly investigated by excellent observers.* A disposition has recently been evinced to seek the actual cause of lead atrophy† in an *affection of the ganglion-cells situated in the anterior horns of the cervical cord*, and to regard the degeneration and atrophy of the nerves supplying the extensors and consequent wasting of the muscles themselves as effects of the central lesion. True, by this hypothesis, the question of the cause of the localisation is merely shifted, not explained. Some writers,‡ moreover, have not been able to convince themselves that the spinal cord is really involved; they are disposed rather, from their own researches, to look upon lead atrophy as a strictly peripheral affection, and hold the process to be a peculiar degenerative *myositis* or *neuritis*. As regards the atrophy of the thyroid after the use of iodine, no attempt even has been made at formulating a theory. There is certainly no predilection causing the iodine to be deposited in the tissues of the thyroid; and we are almost forced to assume a peculiar sensitiveness of its elements to iodine, resulting in a lessened capacity for assimilating nourishment.

A part undergoing simple atrophy is *smaller*, much *firmer*,

* Tanquerel des Planches, 'Traité de maladies de plomb.,' Paris, 1839, ii; Duchenne, 'Electrisation localisée,' 3me éd., Paris, 1872, p. 677; Gusserow, 'Virch. A.,' xxi, p. 443; Hitzig, 'Studien über Bleivergiftung,' Berlin, 1871; Heubel, 'Pathogenese und Symptome d. chron. Bleivergiftung,' Berlin, 1871; Bernhard, 'Arch. f. Psych. und Nervenkrankh.,' iv, p. 601; Westphal, ibid., p. 776.

† Erb, 'D. A. f. kl. Med.,' iv, p. 242; 'Arch. f. Psych. u. Nervenkrankh.,' v, p. 445; in Ziemssen's 'Hdb.,' xii, 1; E. Remak, 'A. f. Psych. u. Nervenkrankh.,' vi, p. 1, ix, p. 510; C. v. Monakow, ibid., x, p. 495.

‡ Lancereaux, 'Gaz. méd. de Paris,' 1862, p. 709, 1871, p. 383; Gombault, 'Arch. de physiol. norm. et pathol.,' v, p. 592; 'Progrès méd.,' 1880, No. 10; Friedländer, 'Virch. A.,' lxxv, p. 24; Zunker, 'Ztschr. f. klin. Med.,' i, p. 496; Moritz, 'Journ. of Anat. and Physiol.,' xv, p. 78.

and *tougher* than normal. Its dryness and density are also increased as a rule. The other naked-eye characters of an atrophic organ obviously depend on its anatomical structure, and to a less extent on the distribution of the atrophy. All the constituent parts of the organ may be affected, or only some of them; in the former case the surface of the organ remains smooth, in the latter it becomes uneven. When the atrophic indentations of the surface are shallow but numerous the condition is termed granular atrophy. The folding and wrinkling of the skin or of a membrane from atrophy of the subjacent tissues in which the skin or membrane itself does not participate need hardly be dwelt on here; its occurrence is sufficiently testified to by the wrinkles in the faces of old persons after the underlying fat has disappeared, and by the shrivelled appearance of the capsule of an atrophied spleen. As regards the microscopic appearances, many authors, following Virchow's example, distinguish two forms, in one of which the constituent elements of the atrophied part themselves becomes smaller, while in the other their number is reduced. To the first form they apply the term *true atrophy*, or simply atrophy, and to the second, in which there is a numerical decrease, *aplasia*. Our experience teaches on this point that in some organs—the spleen and skin for example—however marked may be the atrophy, the dimensions of the pulp-cells and cells of the epidermis and cutis continue normal. In others—the liver and more especially the muscles—the converse is the case; for here the diminution of the organ is inaugurated by an actual diminution in size of the elementary parts, hepatic cells or muscle-fibres. So soon, however, as the atrophy of these organs has reached a certain pitch, a numerical decrease invariably occurs. As a matter of fact the distinction depends solely on the laws of growth of the respective organs. The cells of the spleen-pulp and epidermis are not appreciably smaller in children than in adults; and thus the spleen and skin grow by the addition of new elements. On the other hand, the muscle-fibres of a child are narrower than those of a grown person; though, it is true, an adult muscle contains a larger number of fibres than does the same muscle during childhood. The events occurring in atrophy of single organs

harmonise perfectly with the laws of growth just explained. Moreover, the distinction between atrophy and aplasia is meaningless unless we look upon the organs as stable structures, a consideration which relieves us of the necessity for further discussion. To those, however, who regard the organs as nothing more than cell-aggregates whose duration of life is comparatively brief, and existence at any rate transitory, atrophy apart from deficient cell-formation, *i. e.* without aplasia, is impossible. More interest attaches to certain other details which are revealed by microscopic examination of atrophic tissues, though so far we have failed to throw light on their connection and significance. We are still ignorant of the cause to which the peculiar fibrillation of the ground substance of hyaline cartilage, such as occurs, *e. g.* in senile marasmus and arthritis deformans, should be ascribed. Nor are we better informed as to the origin of the proliferation of nuclei described by Flemming,* or of the small, round, granular cells found in fat-cells which have partly or completely lost their fat. It is possible that an *atrophic proliferation* of this kind is not confined to adipose tissue. In atrophic muscles—in ankylosis of the knee-joint and the like—one often meets with such multitudes of muscle-nuclei that some such assumption appears justifiable.

The degree of the atrophy depends essentially on the intensity of the agent determining it. It may be said generally that local are more pronounced than general atrophies, and that, of the local atrophies, those involving organs of vital importance will, for obvious reasons, be less marked than where less important structures are implicated. It will also appear natural that the passive atrophies should be as a rule more extreme than the active, or at any rate should become so. Muscular atrophy following ankylosis of the knee-joint is severer in proportion to the acuteness of the angle at which the knee is fixed; for the obstruction to the blood-supply will then be greater, and thus with the inactivity a second factor, local anæmia, becomes associated. Should active atrophy occur in very early life, as in the thymus or the membrana pupillaris, it can, as already stated, result in the complete disappearance of the organ or part. For reasons not far to seek,

* Flemming, 'A. f. mikr. Anat.,' vii, pp. 32, 328; 'Virch. A.,' lii, p. 568.

all atrophies, physiological or pathological, are in general more marked the earlier they set in. In the organs of a child, indeed, no actual diminution is needed to make later on the impression of marked atrophy; insufficient growth is enough. For it is unnecessary to point out that *e. g.* the infantile genitals, or the narrow and thin-walled aorta of a woman are essentially identical with the common atrophies just discussed; here just as there the atrophy is the result of an abnormally reduced apposition of new tissue-elements.

The influence of atrophy on the functions of the various organs will be discussed in connection with the pathology of the latter. As for the atrophic disturbances of nutrition affecting the vascular system, such as deficiency of blood, abnormal thinness of vessel walls, and above all atrophy of the cardiac musculature, we have already thoroughly dealt with their influence on the circulation. But let us briefly apply our recently acquired knowledge to atrophy of the heart. There is no such thing, I need hardly say, as an active atrophy of the heart; even senile atrophy does not occur in the organ, for owing to the gradual dilatation of the arteries in old age, the heart undergoes a slight hypertrophy. But passive atrophy is certainly met with, and may either be partial and circumscribed, in consequence of sclerosis or occlusion of the coronary vessels, or general as the result of inanition, however conditioned. As regards general atrophy, though it is often extreme, I have repeatedly had occasion to notice that the lowering of the heart's energy which undoubtedly follows it has no effect on the velocity of the circulation. This is due to the fact that it invariably forms part of an atrophy in which all the tissues are engaged, and in which consequently the blood-mass is also diminished.

There is still a subject to which with your permission I should like to refer, namely, the great importance of atrophies on which other atrophies are in a sense conditional. If the processes here concerned were merely such as the falling off of the hair on atrophy of the hair-follicles—which as you know is commonly a senile change—or imperfect growth of the long bones after atrophy of the epiphysial cartilages, I should hardly consider it necessary to call attention to them. Similarly, it might better be left for pathological anatomy to

discuss in how far aplastic processes in so-called "mother organs" are influential in giving rise to some of the forms of arrested development, and whether or not early atrophy of cartilage constitutes the determining cause of cretinistic and other deformities of the skull. I desire, however, to direct attention to the extreme importance of muscular conditions during the period of growth, inasmuch as these affect the skeleton and by consequence the whole body in its development; the growth of the extremities being more especially determined by them. Mere inaction of muscles as the result of paralysis is attended by an atrophy which is either slight or remains so for a considerable time; and yet it is capable of exerting a disturbing effect on the growth of the bones to which the muscles in question are attached. This is due in all probability to the absence of that active muscular congestion, in the benefits of which the bones would normally participate. But when, as often happens, the atrophy associated with paralysis of muscles becomes marked, the reaction on the bones is much more considerable. The impulse toward growth communicated to the bones by the elongating muscles is to a certain extent wanting. Moreover, the statical purposes which it is the office of bone to fulfil become void by atrophy of the muscles. These factors are enough to account for the scanty deposition of osseous material, and, since resorption continues, for the shortness and thinness of the bones. In these cases the medulla is usually over-developed and loaded with fat, and the compact substance very slender. The growth of the skin naturally keeps pace with that of the bone; and thus when muscular atrophy has set in in early childhood the length and girth of the affected extremity may fall far short of the normal. The cause of the primary atrophy is quite immaterial. Dwarfing of an extremity is no more marked when the result of infantile paralysis than when due to early acquired ankylosis of the hip-joint. It may indeed be unusually pronounced, if the principal blood-vessels of the limb undergo compression through the contraction of the tissues in proximity to the joint during the course of the chronic inflammation.

Lastly, we have to consider a number of atrophies not

included in any of the foregoing categories. As proposed by Romberg* and Virchow,† they are classed together as *neurotic atrophies* or simply *trophoneuroses*. If indeed it be meant to convey that these atrophies result directly from primary disturbances of innervation, the *congenital defects* at least must be dissociated from them. For to say nothing of the absence or extreme dwarfing of the whole or part of an extremity, we are by no means justified in concluding with regard to those interesting cases where certain nerves and their corresponding voluntary muscles are together wanting, that the failure of the latter to develop is due to the absence of the nerves. Perhaps the converse might, with equal correctness, be maintained; and it is more judicious, or rather only right, to look upon the absence of muscles and nerves as the conjoint effect of a disturbance of the embryonic rudiments of both. There is perhaps better ground for placing the *crossed unilateral atrophies* among the trophoneuroses. In these cases we find atrophy of one cerebral hemisphere associated with atrophy of the corresponding half of the head and the opposite half of the trunk and extremities. In addition there is sometimes seen an atrophy of the side of the cerebellum opposite the diseased cerebral hemisphere, and a corresponding asymmetry of the spinal cord has even been observed. Yet these extremely striking forms have no real claim to a special position, since they depend ultimately on the development at an early period of existence of unilateral affections of the brain, such as hydrocephalic atrophy; these in their turn lead to unilateral paralysis and consequent imperfect growth of parts. In a word, we have here an exquisite example of secondary atrophy of the variety just discussed. In a third form, usually regarded as a trophoneurosis, the so-called *circumscribed atrophy*,‡ the indications of a dependence on nervous influence are very far from definite or convincing. It most often affects one side of the face, but is occasionally observed in other situations. It occurs in young persons as a highly insidious atrophy of the subcutaneous

* Romberg, 'Klin. Ergebnisse,' ges. v. Henoch, Berlin, i, 1846, ii, 1851.

† Virchow, 'Hdb.,' i, p. 318.

‡ Literature, *vid.* Eulenburg, Ziemssen's 'Hdb.,' xii, 2, p. 54; also Emminghaus, 'D. A. f. kl. Med.,' xi, p. 96.

fat, of the skin, underlying bones, and less commonly of the muscles. But no anatomical examination has been made into its pathology, and though the fact that it is unilateral, and the occurrence of many peripheral and central disturbances of innervation, both before and during the progress of the disease, point undoubtedly to participation of the nerves, yet it is by no means proved that a nervous affection is actually the causal factor in the atrophy.

Not till we come to consider the *atrophic paralyses*, or atrophies so extremely common in paralysed muscles and nerves, have we a fairly secure foothold. You are probably somewhat surprised at my referring again to these atrophies after having already dealt with them as atrophies of inaction. It is in fact only very recently that we have succeeded in separating from the great bulk of muscular atrophies due to inactivity a certain group whose distinctive character is the rapidity and intensity of the resulting atrophy. When an extremity is kept for several weeks in a rigid bandage of plaster of Paris, the muscles, it is true, lose considerably in bulk. This loss is not, however, for a moment to be compared with that taking place during an equal period in certain diseases of the cord and in some peripheral paralyses. There is a very evident difference between these atrophic paralyses and the atrophies of inaction. The decrease in volume of muscles paralysed, for example, from cerebral disease is always moderate in degree, while the nerves themselves never atrophy, even though the hemiplegia has existed for years unchanged. Consider, on the other hand, a *peripheral paralysis*—to take the simplest case—as the result of injury to a motor or mixed nerve. To me it seems questionable whether one is justified in referring all the events taking place when a nerve is crushed or divided to the atrophy alone. After such an accident there speedily occurs, as you know, a peculiar so-called coagulation of the medullary sheath, which has given rise to much discussion; and, associated with it, the development of the characteristic myelin-forms. Their development is a preliminary to the gradual disintegration of the contents of the nerve-fibres into smaller and larger clumps and irregular droplets. After the first week unmistakable globules of fat make their appearance between the drops of myelin; their number increases at

the expense of the latter. In this manner the nerve-contents continue to be transformed into a conglomeration of fat-globules and structures similar to Gluge's corpuscles up to the third week, when they begin to disappear. While this is taking place in the medullary sheath, the axis-cylinder first swells considerably, probably from imbibition of lymph, and then slowly undergoes resorption, and there finally remains a narrow, pale, irregular, undulating band, in which as a rule, no trace of an axis-cylinder can be detected. What events in the series should be attributed to direct injury of the nerve-contents, and what to the interruption of connection with the central nervous system, must be left undecided, more especially since some other appearances, such as the presence of numerous lymph-corpuscles in the delicate connective tissue between the nerve-fibres, point to the existence of an inflammatory process. In any case the final result is *a nerve-atrophy*. It occurs even in the so-called rheumatic paralyses—where no appreciable direct trauma affects the nerves—provided they have lasted for a certain time. *Pari passu* with the degeneration and atrophy of the nerve-fibres there invariably takes place an atrophy of the muscles supplied by them. The muscular atrophy sets in as early as the first week, and before a month has elapsed is usually so considerable as to have caused a reduction of the organs to about half their former thickness. The reduction is the result of a genuine indubitable atrophy. Multiplication of the nuclei occurs as a rule, and is probably analogous to the atrophic proliferation of fat-cells. Moreover, chronic inflammatory processes in the inter-muscular connective tissue are frequently associated with the atrophy of the contractile substance; at any rate, the connective tissue is increased. The subsequent changes in the atrophied muscles depend upon the occurrence or non-occurrence of regeneration of the nerves. In the former case the muscular atrophy gradually passes off and the muscle regains its normal condition; in the latter the disease slowly advances till at last all but a vestige of the contractile tissue has disappeared.*

* Waller, several papers in 'Compt. rend.,' xxxiii and xxxiv, 1851 and 1852; 'Lond. Journ. of Med.,' 1852; Schiff, 'A. f. phys. Heilk.,' xi, p. 145; 'Lehr. d. Phys. d. Menschen,' i, p. 111, Jahr 1858; Mantegazza, 'Gaz. med.

Analogous changes have recently been observed in certain *spinal diseases,* and the similarity has been found to extend even to many details. But the resemblance is very far from prevailing in all affections of the spinal cord, even when accompanied by paralysis of motion. Rather, it is found in diseases differing greatly *per se,* but having in common the implication of a definite region of the cord, namely, *the large groups of ganglion-cells in the anterior cornua,* or (in the medulla oblongata) of *Stilling's nuclei,* in particular the nucleus for the hypoglossal. Some of the diseases in question are acute, such as *infantile paralysis,* the analagous disease of *adults,* and *acute bulbar paralysis.* Some no less typical forms are markedly chronic, but at the same time distinctly progressive, namely *progressive muscular atrophy* and *progressive bulbar paralysis.* You will not expect me to sketch for you, even hastily, a picture* of these highly interesting affections; this is the office of special nervous pathology. For us it will be amply sufficient to throw into relief their points of relationship to muscular and nervous atrophy. The occurrence of such atrophy is pathognomonic of all these diseases. In the bulbar affection the muscles of the tongue, palate, and lips, together with the n. hypoglossus, accessorius and facialis supplying them, are implicated. In infantile paralysis and progressive muscular atrophy the voluntary muscles with their nerves are involved to a greater or

ital. Lombard.,' 1867; Vulpian, 'A. d. Phys.,' 1869, Heft 5; Erb, 'D. A. f. kl. Med.,' iv, p. 535, v, p. 42; Neumann, 'A. d. Hlk.,' ix, p. 193; 'A. f. mikrosk. Anatomie,' xviii, p. 307; Ranvier, 'Compt. rend.,' lxxv, p. 1831, lxxvi, p. 491; Bizozzero u. Golgi, 'Wien. med. Jahrb.,' 1873, p. 125; Engelmann, 'Pflüg. A.,' xiii, p. 474, xxii, p. 1; Dobbert, 'Ueber Nervenquetschung,' I.-D., Königsberg, 1878; Colasanti, 'A. f. Anat. u. Phys.,' 1878, Phys. Abth., p. 206; Korybutt-Daszkiewicz, 'Ueber d. Degeneration u. Regeneration d. markhaltigen Nerven nach traum. Läsionen,' I.-D., Strassburg, 1878; Rumpf, 'Untersuch. aus d. Heidelb. physiol. Institut.,' 1879, ii, p. 307; for numerous references, more especially to the older literature *vid.* Eichorst, 'Virch. A.,' lix, p. 1, and Erb, in Ziemssen's 'Hdb.,' xii, 1, p. 360.

* Duchenne, 'Électrisation localisée;' Charcot, 'Leçons sur l. maladies de système nerv.,' sér. i et ii, 1874; Leyden, 'Klinik d. Rückenmarkskrankh.,' Berlin, 1876, ii, p. 469—also ref. to Lit.; Kussmaul, 'Sammlung klin. Vorträge,' No. 54, Leipsig, 1873; Erb, in Ziemssen's 'Hdb.,' xi, 2, Zweite Aufl., 1878.

less extent; the change being sometimes most marked in the upper extremities, sometimes in the lower, and often very striking in the trunk and neck. The function of the affected muscles is always greatly prejudiced in these diseases. As a rule, indeed, the paralysis precedes the atrophy; and in this way muscles which have sustained but a slight decrease of volume may have almost completely lost their functional power. On microscopic examination of the paralysed muscles and nerves, changes are observed which, as already stated, bear a marked resemblance to those of traumatic paralysis. According to the stage of the disease, the nerves and muscle-fibres appear more or less narrowed, or have vanished completely. Of such muscle-fibres as still survive, an occasional one is fattily degenerated, but the great majority have undergone simple atrophy; while at the same time the muscle-nuclei are unnaturally abundant. The inter-muscular connective tissue, on the contrary, does not take part in the atrophy; more than this—it has usually increased in bulk. Not uncommonly too there is within its meshes such an accumulation of large fat-cells that to the naked eye the muscles look like masses of fat, with here and there a pale red streak or two serving to recall their original structure. This appearance may sometimes be observed in all possible forms of muscular atrophy, *e.g.* after ankylosis. Turning from paralytic atrophy as it affects the muscles and nerves to the changes revealed by anatomical examination of the spinal cord, we find that they are due to very different processes. These are *acute* and *chronic inflammations, softening,* and, most commonly in the chronic, progressive forms, that peculiar change which is usually termed *sclerosis* in the central nervous system. In every case, however, the lesion is situated at the anterior cornua and Stilling's nuclei, for the spinal cord and medulla oblongata respectively. As to the chronic cases, whether so from the first or originating acutely, almost all the most recent observers are unanimous in stating that *the ganglion-cells of the anterior cornua or of Stilling's nuclei are atrophied, shrunken, and in the most severe examples no longer to be detected in many situations.* In addition there is found as a rule a more or less marked atrophy of the corresponding anterior roots. Basing his conclusion on

these facts, Charcot was the first to assume that the multipolar ganglion-cells, just mentioned, are not only motor, but at the same time, trophic centres for their motor apparatus, *i. e.* for the nerve-fibres arising from them and for the muscles supplied by the latter. This view, it is true, is not without its opponents. Above all Friedreich* has endeavoured to show that progressive muscular atrophy originates in *a primary interstitial inflammation of muscle* followed by atrophy of the muscle-fibres through contraction of the new-formed tissue. The atrophy of the nerves and the central degenerations are regarded by him as mere secondary effects of an ascending neuritis determined by the myositis. That *secondary atrophy of the spinal cord* may, in fact, become associated with an acquired primary dwarfing, or with loss of an extremity, is established beyond doubt by a number of careful observations. Vulpian, Dickinson, Leyden, Charcot† have found atrophy of the corresponding side of the cord in persons who long before have had an extremity removed by amputation; and Déjérine‡ made a similar observation in a person forty years old, who had a club-foot from childhood. In some cases the atrophy involved the white and grey substance, but oftener only the anterior cornua with their ganglion-cells in the corresponding enlargement. Now the atrophic changes observed in such cases do not admit of comparison with the lesions found in the medulla oblongata in atrophic paralyses proper. Nor does Friedreich's view explain the instances in which anatomical examination reveals severe atrophy of the muscles, and degenerative changes in the ganglion-cells of the cord, but nothing of a pathological character in the corresponding peripheral nerves and anterior roots.§ Yet we must undoubtedly endorse the opinion of Friedreich that cases of progressive muscular atrophy occur in which no morbid alteration of the anterior cornua is per-

* Friedreich, 'Ueber progr. Muskelatrophie, über wahre und falsche Muskelhypertrophie,' Berlin, 1873.

† Vulpian, 'Arch. de phys.,' 1868, p. 443; 'Compt. rend.,' 1872, p. 624; Dickinson, 'Transact. of the Path. Soc.,' 1873; Genzmer, 'Virch. A.,' lxvi, p. 265; Leyden, 'Klinik,' ii, p. 316; Charcot, 'Progrès méd.,' 1878, Nos. 3—5; Dreschfeld, 'Journ. of Anat. and Phys.,' xiv, p. 426.

‡ Déjérine, 'Arch. de phys.,' 1875, p. 253.

§ Cf. *e.g.* the case of Erb and Schultze, 'A. f. Psych.,' ix, p. 369.

ceptible however carefully the cord be explored. I can myself bear testimony to a case of this kind, which Lichtheim* has examined and described. With regard to this disease, then, it must be the aim of subsequent investigation to decide whether it does not perhaps include two distinct processes, a primary spinal and a primary myopathic. But though the reserve which causes some German writers to hesitate before placing progressive muscular atrophy among the paralyses of spinal origin is no doubt prudent, there is no sufficient argument against the applicability of Charcot's hypothesis in general. For how are infantile and acute bulbar paralyses, where the loss of motion is so exquisitely marked from the first and invariably precedes the muscular atrophy, to be explained unless on the assumption of a primary spinal affection? Add to this the fact to which attention has been called more particularly by Leyden—that in all possible varieties of chronic and acute disease of the spinal marrow a paralytic atrophy develops when the affection has extended to the groups of ganglion-cells in the anterior cornua, and to me it seems that the evidence for Charcot's hypothesis is as convincing as, short of actual experimental proof, it could possibly be. If so, a very high degree of general pathological interest attaches to the atrophic paralyses. For they prove that nervous connection with a centre performing its functions normally is indispensable to the maintenance of a normal state of nutrition in the organ or tissue, and *that the centre is therefore undoubtedly a trophic one.* On the other hand, we should not be justified in concluding that, because interruption of nervous connection with the ganglion-cells of the anterior cornua, or the atrophy and disappearance of the latter, is followed by muscular atrophy, a similar relation holds true of all the remaining tissues. Bear in mind what I more than once referred to in the introduction to this section, namely that the relation of the multipolar ganglion-cells to the motor nerves and to the muscles is specially intimate and perfectly unique. The only other relation at all comparable to this one is that of some glands to their secretory nerves; and here too we are acquainted with facts which may without violence be referred to a dependence on trophic in-

* Lichtheim, 'A. f. Psych.,' viii, p. 521.

fluences.* The non-existence of such a relationship in all kinds of connective tissue, skin, bones, &c., is nowhere more apparent than in these very atrophic paralyses. For in cases where only slight vestiges of the muscle still remain, the skin with the hairs, nails, and glands, as well as the bones, present scarcely perceptible deviations from the normal—deviations which no one would hesitate to attribute simply to inactivity or to interference with vascular innervation. As regards the intermuscular connective tissue, I already told you that it not only does not participate in the atrophy of the muscle-fibres, but, on the contrary, *increases in bulk* and very frequently *becomes infiltrated with fat.*

I mentioned that *saturnine atrophy of the forearm extensors* has recently been interpreted by some as a trophoneurosis belonging to the group of atrophic paralyses just discussed. The muscular atrophies which sometime appear *in the train of acute diseases, e. g.* typhoid fever, and involve isolated regions, or the muscular system generally, also appear to depend on spinal causes, and to take their place in the series of processes which have now engaged our attention. This group of true neurotic muscular atrophies is, you perceive, by no means a small one; and accumulated experience on this subject affords sufficient ground for inquiring in every case of severe muscular atrophy whether there exists a primary disease of the anterior cornua or not. We must bear in mind, however, that besides the passive, active, and spinal muscular atrophies, *independent forms* of unknown origin may possibly occur. It is highly probable, as already stated, that some of the cases now termed progressive muscular atrophy should really be looked upon as independent forms. But disregarding these, we find, in *pseudo-hypertrophy* or *lipomatous atrophy of muscle,*† a disease in which the affected muscles display a combination of the *most extreme atrophy of the fibres with enormous growth of intermuscular fat;* while in the few instances‡ where an examination of the nerves and spinal cord could be carried out, no kind of pathological change was de-

* Schauta, 'Wien. akad. Stzgsb.,' lxv, Abth. 3, p. 105, 1872.

† Lit. see Eulenburg, Ziemssen's 'Hdb.,' xii, 2, p. 149, and especially Friedreich, 'Progr. Muskelatrophie.'

‡ Eulenburg und Cohnheim, 'Verhdl. d. Berl. med. Ges.,' 1866, p. 191;

tected. Should these observations be confirmed by future investigation, we have, in my opinion, no resource but to assume the existence of *an idiopathic affection of muscle,* which leads to a simultaneous atrophy of the contractile substance and hypertrophy of the intermuscular adipose tissue.*

Charcot, 'Arch. de phys.,' 1872, p. 228; Brieger, 'D. Arch. f. klin. Med.,' xxii, p. 200; Schultze, 'Virch. A.,' lxxv, p. 475.

* On the subject of Simple Atrophy consult further Virchow, 'Hdb.,' i, p. 303; C. O. Weber, 'Hdb.,' i, p. 305, &c.

CHAPTER III.

PATHOLOGY OF THE INORGANIC CONSTITUENTS OF THE TISSUES.

Physiological importance of the inorganic salts.—Consequences of deficient supply of alkaline and earthy salts to the organism.—Rachitis and osteomalacia.

Anthracosis, siderosis, and chalicosis of the lungs.—Argyria.

Calcification.—Calcareous metastases.—Petrifaction of dead and obsolete tissue.—Senile calcification of the blood-vessels.—The arteries chiefly affected.—Calcification of the glomeruli.—Ossification of permanent cartilage.

Calcareous concretions, more especially as the result of bacterial action.

We now come to that group of nutritive derangements which is characterised by an *alteration in the chemical composition* of the tissue-elements. The change may be due either to a quantitative disproportion between the various constituents or to the appearance of new abnormal materials. These derangements, which are collectively known as *degenerations* or *degenerative atrophies,* play a very important part in pathological anatomy and histology; nor can we dispense with a minute discussion of them, if for no other reason, because of their extreme frequency. I may as well confess at once that the results of our discussion will not be very satisfactory. For here, if anywhere, our insight into the intimate connections of the processes has failed to keep pace with our knowledge of their morphology. And yet there is no department in which the importance, indeed necessity, of a chemical interpretation is so apparent as here. Every step in this direction

has, as you will soon see, opened up new points of view; while whenever the chemical processes are still enveloped in obscurity we are hopelessly incapable of explaining the facts.

In the structure of the animal body and all its parts there is included, you are aware, a certain quantity of *inorganic salts,* the so-called *ash-constituents.* While their distribution throughout the various organs is very unequal, the corresponding organs of different individuals of the same species always yield approximately equal percentage contents. Nowadays we do not require to prove that the presence of these constituents is no mere accident; they are no less indispensable to the building up of the organs and tissues than are the organic substances themselves. They must obviously then be subject to a metabolism by which they are used up and finally excreted; and it is plain that the necessary permanence of the body in saline materials can only be secured by the continuous supply of fresh quantities with the food. Now, it is customary, following Liebig's example, to claim for some of the salts a *histogenetic* function in a strict sense, inasmuch as they unite with the albumen and thus actually go to build up the organs. The importance of the other saline constituents is said, on this view, to consist principally in their conditioning the *chemical reaction* of the fluids in which they are dissolved. Yet though there is no fundamental objection to such a distinction, it has manifestly no more than a theoretical value, simply because the salts which at one time form undoubted constituents of the tissues must at another circulate dissolved in the organic juices. Each atom of calcium phosphate must have formed a dissolved component of the blood before it could enter the bones; and conversely a portion of the lime excreted with the urine must have previously taken part in the structure of the skeleton. What is true of the lime-salts holds true of all the other saline constituents. The salts which circulate in the fluids are identical with those which contribute to the building up of the tissues histogenetically. Just as the organism has at its disposal means by which salts insoluble in water can be dissolved in its fluids, so there are almost no tissues, indeed no cells, which do not contain enough water to convert the soluble salts into integral constituents of themselves.

Such being the case, it is evident that adequate supplies of *alkaline* and *earthy salts* are equally important for the nutrition of the tissues. If one or other or both be absent from the food, *the growth and repair of the tissues must be essentially impaired.* This is no longer a mere *a priori* conclusion. As for the alkaline salts, good care is taken in ordinary circumstances that they shall be present in human food, and as they are very soluble, no digestive disturbance can hinder their absorption while the organic constituents are being digested. On the other hand, it has recently been shown in several series of experiments by Kemmerich,* and in a particularly painstaking manner by Forster,† that the organism cannot continue to exist if the supply of alkaline salts be reduced below a certain minimum. The withdrawal of potash salts or of chloride of sodium from the food of young dogs is followed by emaciation, and this result is not owing to any interference with digestion through the absence of saline matters, nor does the metabolism take place in abnormal fashion. No digestible particles appear in the fæces; the urine does not contain either albumen or products of abnormal decomposition like leucin or tyrosin. The animals no longer put on flesh, because cells and muscle-fibres cannot be built up from albumen and other organic nutritive materials in the absence of the salts which are integral constituents of the cells and fibres. But though the supply of salts be inadequate or *nil*, the excretion of saline matters does not therefore cease; it becomes less than normal, it is true, but is always considerably in excess of what is taken with the food. The source of this *plus* is plain enough. The salts are withdrawn from the tissues, and thus it is intelligible that young animals, in whose food they are deficient, do not merely fail to put on flesh, but, like full-grown animals in similar circumstances, cannot even maintain their condition intact. The muscles appear to be affected very early, and after them the central nervous system. The animals become weak, dull, and apathetic. Later on, other functional derangements, more especially of the digestive organs, set in. When this point is reached, dogs, as well as pigeons, vomit what-

* Kemmerich, 'Pflüg. A.,' ii, p. 49.

† Forster, 'Zeitschr. f. Biol.,' ix, p. 297, xii, p. 464.

ever food is given them ; they become extremely emaciated and generally decrepit, and at last perish convulsed.

It is obvious that in these cases the ash contained in each of the tissues will, at the conclusion of the experiments, be reduced below the normal standard. On bearing in mind how extremely minute must be the quantity which is yielded by the majority of organs, you will not expect the falling-off to be recognisable in the individual cells or muscle-fibres. Not even in the bones can an evident effect be detected when the animals are completely or almost completely deprived of salts ; for death then occurs at a time when the bones have lost very little of their saline constituents. Not so when the food of the animals contains alkaline, but not *earthy salts.* True this also has been disputed. Weiske and others* believe that the composition of bone, both in fully grown and in growing animals, is completely uninfluenced by a diet rich or poor in lime or phosphoric acid ; and a similar conclusion has been come to by Zalesky†. Now, it is certainly true that the composition of osseous tissue is not in the least altered by giving an excessive amount of phosphoric acid or lime to the animal with its food. For the organic osseous substance yielding gelatine, the so-called bone-cartilage unites with the bone-earth in certain definite proportions which are not at all affected by the presence of a little more phosphoric acid or lime in the intestinal canal or circulation. But this by no means implies that lime-salts can be deposited in the bones except they be supplied to the organism from without ; to suppose so would be to fly in the face of all our other notions on the subject of nutrition ! Now, as a matter of fact all criticism of this theory is superfluous. For a number of careful experimenters, Chossat,‡ Bibra, Wegner,§ Voit,|| and others, have repeatedly shown in the most positive manner *that the bones of animals become poor in earthy salts and by consequence thin*—they may even be soft and pliable when the

* Weiske, 'Zeitschr. f. Biol.,' vii, pp. 179, 333 ; Weiske und Wilde, ibid., ix, p. 541.

† Zalesky, Hoppe-Seyler's 'Med. chem. Unters.,' 1866, Heft i, p. 19.

‡ Chossat, 'Compt. rend.,' 1842, T. xiv, p. 51.

§ Wegner, 'Virch. A.,' lv, p. 11.

|| E. Voit, 'Zeitschr. f. Biol.,' xvi, p. 55.

deficiency of lime is great—*if they are supplied with a food containing all the other constituents in sufficient quantity, and but little or no earthy salts.* These results are most striking in birds, owing to the activity of their osseous metabolism. Further investigation of the details is necessary before we can say whether this impoverishment affects all the bones equally, or whether some lose their lime-salts earlier or in larger quantity than others. It appears not improbable *a priori* that those which happen to be chiefly employed, and whose metabolism is therefore most active, should behave differently in this respect to the rest of the skeleton. This idea is supported by many facts from human and animal pathology.

For in man and in certain species of animals, with bony skeletons, there occur certain diseases, *in which the bones contain less lime-salts than normal,* and are therefore more brittle or more pliable, and certainly softer than in a normal state. When it affects young individuals *whose skeleton is still growing,* the disease is called in the human being *rachitis;* while in the young of the mare, cow, sheep, swine, goat, and beasts-of-prey in our menageries it is technically termed "the lameness" (*die Lähme*). So long as this affection continues the bones do not acquire the hardness characteristic of them. On the other hand, we speak of *osteomalacia* when bones which have already acquired their normal hardness become soft and fragile. Such a reduction of natural firmness is extraordinarily common in extreme old age, and forms one of the manifestations of senile atrophy, when it also obtains the name of *halisteresis* or *senile osteomalacia.* But it occasionally appears in individuals in the prime of life, and, compared with the senile affection, is a decidedly *acute* disease, being sometimes even accompanied by pyrexia and violent pains in the affected bones. This disease—*osteomalacia* in a strict sense—besides occurring in human beings, is observed in cattle and goats and sometimes in giraffes and herons confined in menageries and zoological gardens. It is identical with what is known to veterinarians and cattle-breeders under the name of "*bone-brittleness*" (*Knockenbrüchigkeit*). Senile osteomalacia is for obvious reasons almost exclusively confined to man.

I feel compelled, disregarding the differences which these diseases display amongst themselves, to deal with them collectively in this place, because they have in common one character which at present engages our attention, namely, the abnormally slight degree of cohesion and hardness of the bones. That this depends essentially *on a deficiency of bone-earths* is self evident; it has, moreover, been positively proved by numerous analyses of the bones in rachitis and osteomalacia.* A reduction of the inorganic constituents to one *half,* even to a *third,* the normal is by no means rare in extreme degrees of osteomalacia, and has often been found in rachitic bones. A detailed description of the course and morbid anatomy of these diseases would naturally be out of place in these lectures. It will be quite sufficient for our present purpose to determine the morphological condition of the skeleton in rickets and osteomalacia; in other words, to explain the manner in which the want of earthy salts is manifested in the structure of the bones. Please bear in mind once for all that, in rachitis and osteomalacia respectively, those parts of the skeleton which are *already* fully matured or *still* remain intact are composed of gelatine-yielding material and bone-earth, combined in *precisely the same proportions* as in normal bone at a corresponding period of life. The defect must therefore consist in a deficiency of fully developed bone or in the substitution for normal osseous tissue of a material containing a much smaller amount of earthy salts. But what is the nature of this material? In rachitic bones there is found at the junction of epiphysis and diaphysis, as well as immediately beneath the periosteum,—in every situation, in short, where new bone should be formed, a more or less compact soft material, which is sometimes gelatinous, varies in quantity with the intensity of the disease, and is known as *osteoid* tissue. This tissue is nothing more or less than *the organic ground-substance of bone without the bone-earth which should be combined with it.* In senile osteomalacia the condition of affairs is quite different. Here both the compact substance and the trabeculæ of the spongy parts

* Analyses by Gorup-Besanez, 'Phys. Chemie,' 2 Aufl., p. 580, and by Senator, in Ziemssen's 'Hdb.,' xiii, p. 1; here also *vide* complete literature of Rachitis (p. 154) and Osteomalacia (p. 195).

are everywhere extremely thin, forming delicate laminæ, while the space which should properly be occupied by osseous tissue is filled with fat-cells. As to the histological appearances of the bones in true osteomalacia, I can offer no opinion from personal observation, since the disease does not occur in this part of the country. But according to the statements of competent authorities* they consist in the substitution of *osteoid zones* for typical osseous tissue. These zones are not, however, situated beneath the periosteum and at the boundaries of the epiphyses, as in rickets, but occupy essentially the interior of the fully formed bone *in immediate proximity to the Haversian canals.* The medulla in this disease is frequently, though not invariably, found to be markedly hyperæmic.

Now, how are these different conditions to be interpreted? Senile softening is least difficult of explanation; for it is evidently the simple expression of *senile atrophy of bone due to failure of apposition.* Whether the disappearance of the osseous tissue occurs at an unusually rapid rate in these cases, owing to some special cause or other, cannot be laid down, at any rate, as a generally applicable rule. The process here, as in all places where bone undergoes resorption, is effected through the agency of the much discussed *giant-cells,* which, it appears, are developed from the vessels.† But the important point, in any case, is the complete failure of bone-production. Taken all in all, the process is identical with the senile atrophy of glands, muscles, &c. With this disease the rickety affection of bones has, as you will perceive, nothing whatever in common. For here the deposition actually takes place in the proper situations; but the deposited tissue is not typical osseous substance, or is so only in parts. The great bulk of it consists of organic ground-substance yielding gelatine, from which the earthy salts are absent. It is not easy to decide whether the production of osteoid tissue is at

* Virchow, his 'Archiv,' iv, p. 307, v, p. 491; 'Cellular-pathologie,' 4 Aufl., p. 529; Roloff, 'Virch. A.,' xxxvii, p. 434; 'A. f. wissensch. u. prakt. Thierheilkunde,' v, p. 152; Volkmann, in Pitha-Billr. 'Hdb.,' ii, 2, p. 342; Rindfleisch, 'Pathol. Gewebelehre,' 3 Aufl., p. 549; Langendorff u. Mommsen, 'Virch. A.,' lxix, p. 452.

† Bredichin, 'Med. Ctbl.,' 1867, p. 563; Wegner, 'Virch. A.,' lvi, p. 523, lxi, p. 44; Kölliker, 'Die normale Resorption des Knochengewebes und ihre Bedeutung, &c.,' Leipsig, 1873; Rustizky, 'Virch. A.,' lix, p. 202.

the same time greater than normal. So far as I see, no such assumption is required to explain the irregular contour of the osteoid layer, its penetration on the one side into the cartilage, and on the other into the fully formed bone. The irregularity becomes intelligible on simply bearing in mind that, *pari passu* with the process of apposition, *resorption is incessantly taking place.* Lastly, we have to determine the nature of the zones of osteoid tissue occupying the interior of the bones in osteomalacia proper. The most widely accepted view is that this tissue originates in an actual decalcification, that normal fully developed bone had previously existed at the seat of the osteoid tissue, and has been deprived of its earth-salts by a pathological process. Accordingly the occurrence is represented as strictly analogous to the method of decalcification adopted with a view to the microscopic examination of bone. Yet for the earthy salts to be separated from the organic basis in this manner the presence of a free acid is absolutely necessary; but though the medulla of the affected bones has been repeatedly examined for it, no such acid has ever been discovered;* it would indeed be no more possible for it to be present than for the blood and transudations of the living body to become acid. Nature adopts a different method in effecting the absorption of bone. The salts are not first extracted and the ground substance afterwards absorbed. Wherever bone disappears, Howship's lacunæ are at once formed and filled with osteoclastic giant-cells. The minutiæ of the process of bone-resorption are indeed still completely unknown to us, but it is certain that *at no stage does an osteoid tissue free from lime occur.* Do not misunderstand me—I do not deny that increased resorption cooperates in the production of osteomalacic changes. This subject must be investigated in the light of our newly acquired experience with regard to the action of the myeloplaques; and the medullary hyperæmia whose existence has been repeatedly demonstrated, would make it probable *a priori* that an abnormally abundant re-

* C. Schmidt, 'Annal. d. Chem. u. Pharm.,' lxi, p. 329; Virchow, his 'Archiv,' iv, p. 262; C. O. Weber, 'Virch. A.,' xxxviii, p. 1; Frey, 'Monatsschr. f. Geburtsk.,' xx, p. 377; Moers und Muck, 'D. A. f. klin. Med.,' v, p. 485; Langendorff und Mommsen, 'Virch. A.,' lxix, p. 452.

sorption of fully-formed osseous tissue does actually occur in this disease. But the osteogenic zones cannot be the effect of resorption; in my opinion they must have originated solely by *apposition.* That the bones are for a long time—certainly till the age of vigorous manhood—the subjects of an uninterrupted and coincident apposition and resorption, from which even the interior of the compact substance is not exempt, is a thoroughly established fact. The distinctive criterion of osteomalacia would accordingly be the apposition of *ground-substance free from earthy salts, i. e.* of osteoid tissue, instead of normal osseous material.

It appears then that rachitis and true osteomalacia are very closely allied diseases, since both depend on *the apposition of an osteogenic substance free from lime in place of typical osseous tissue.* We may in fact dispense with a discussion of their many points of dissimilarity, inasmuch as these may be inferred from the difference in the ages of the individuals affected, *i. e.* from the state of development of the skeleton. For our present purpose the problem reduces itself to the discovery of the *causes,* to which the absence of earthy salts from the new-formed portions of the bone is due. There can be, so far as I see, but two possible causes, namely, 1, an incapacity of the organic ground-substance to enter into combination with and fix the inorganic salts, and 2, a deficiency of earthy salt in the nutritive material supplied to the bones, *i. e.* in the circulating blood. Looking at our problem with a view to these two possibilities, we find that there is not the slightest ground for adopting the former. *There is not a single fact tending to show that the osteoblasts do not produce true osseous tissue when the necessary salts are at their disposal.* But how with regard to the second possibility? In rachitis and osteomalacia have the osteoblasts the required earthy salts actually at command? Cattle-breeders and veterinarians, and foremost amongst them Roloff, long ago asserted most positively that lambs are attacked by rickets when reared by mothers *who themselves feed on fodder poor in lime,* in which their milk will therefore be deficient. But this fact does not rest on their bare assertion. Roloff and others have, at least in my opinion, conclusively proved that the connection exists, more particularly

by the fact of the disease having disappeared from the flocks, on supplying the mothers with suitable (*i. e.* lime-containing) provender, or giving the lambs some additional nourishment rich in lime-salts. Analogous facts are observed in other species of animals liable to be affected with rickets—facts, none of which will perhaps be more interesting to you than the occurrence of rachitis in young lions and leopards, to whom flesh from which the bone has been removed is given as diet.* You will consequently have no doubt as to the existence of similar relations in human rachitis. The idea that unsuitable food plays an important part in rachitis was long ago made probable by the fact that it is distinctly a disease of the proletariat, *i. e.* of those classes of the community where the children get little meat, scarcely obtain pure milk, but live chiefly on vegetables, such as potatoes, &c. Nor is there anything contradictory in the circumstance that rachitis is also met with in children belonging to the well-to-do classes, where it can hardly be supposed that their nourishment is inadequate; for food may be ample in amount and still unsuitable in quality. From our present point of view we regard a dietary as suitable which allows a material containing a sufficiency of lime-salts to be supplied to the bones by the blood. For the question is not whether enough earthy salts are consumed with the food, *but whether they are absorbed in sufficient quantity.* In this respect chronic catarrh or other affections of the digestive organs may be of great importance, more especially those which are associated with a diminution of the acid contents of the gastric juice. But a factor to which attention has lately been directed in Salkowski's laboratory† appears to have still greater influence in the etiology of rickets—namely, the excessive consumption of food rich in potash, and more especially a vegetable diet. For the potassium phosphate of the food seizes on the chlorine of the blood-plasma, and the deficiency of chlorides thus originated is attended by an imperfect production of hydrochloric acid in the stomach, and thus indirectly interferes with the solution and absorption of the lime-salts. It is, therefore, not difficult

* Röll, 'Path. und Ther. d. Hausthiere,' 2 Aufl., p. 411.

† Seemann, 'Virch. A.,' lxxvii, p. 299.

to understand why during active rachitis the urine contains only minimal quantities of earthy salts, although these may be regularly supplied in the food. The absorption of lime-salts is proportionately scanty, so that they fall short of the amount regularly required for the production of new bone. Nothing could more perfectly harmonise with this view than the certainty of recovery when the digestive disturbance is cured and the child supplied with proper food.

In its causation, osteomalacia does not essentially differ from rachitis. Indeed the evidence which Roloff, Haubner,* and others have brought forward for the dependence of the former affection on deficiency of lime in the animal's provender is, if possible, still more convincing than the evidence in rachitis. Nevertheless there has always been the difficulty that adult animals, and above all the carnivora, can, though the supply of lime with the food may be extremely small, maintain their condition unchanged so far as the lime-salts are concerned. It was supposed that even in the most unsuitable foods the earthy salts would not fall below the indispensable minimum; and the result was a renewal of the search after factors which, on the one hand, hinder the resorption of earthy salts, and, on the other, cause their increased separation from the bones and excretion from the body. Feeding with what is called "sour" provender, and in man the consumption of large quantities of sour drinks, *e. g.* must; in short the formation of acid in the alimentary canal has by many been regarded as responsible for these changes. Now the supposed occurrence of a greatly excessive excretion of earthy phosphates with the urine in osteomalacia has never been certainly established.† Moreover, it has been proved, almost to superfluity, by Heiss‡ in Voit's laboratory *that enormous quantities of an acid are unable to deprive the bones of any part of their earthy salts.* His experiment extended over a period of 308 days, during which a small dog was daily given, on the average, 7·4 grams of lactic acid,

* Haubner, 'Jahrb. d. Dresd. Gesellsch. f. Natur- u. Heilk.,' 1876, p. 115.

† Spielmann und Hepp, 'Gaz. méd. de Strassb.,' 1861, No. 8; Pagenstecher, 'Monatsschr. f. Geburtsk.,' xix, p. 128; Moers and Muck, l. c.; Langendorff und Mommsen, l. c.

‡ Heiss, 'Zeitschr. f. Biol.,' xii, p. 151.

amounting in all to 2286 grams, or nearly half its body-weight, but without any influence on the earthy salts. To us who recognise the essence of the osteomalacic derangement to consist in the apposition of osteoid instead of osseous tissue the acid theory is meaningless. We must seek in quite another direction if we wish to solve the problem—how is it possible in the case of adults that a dietary can ever be too poor in lime? Osteomalacia is almost exclusively confined to pregnant or milking cows and goats; and in human beings it is also very rare for other than pregnant women or mothers who nurse their children, to be attacked by it. So close is the connection between osteomalacia and these conditions that it is quite a common thing for the disease to remain stationary or even to heal after the first delivery, and to undergo a fresh exacerbation at every subsequent pregnancy. Pregnancy and lactation involve *a very considerable consumption of earthy salts,* which are appropriated to the development of the skeleton and to the production of milk. If the supply of earthy salts in the food does not undergo a corresponding increase, there is not a sufficiency of material for the apposition of new bone; while, if the deficiency be extreme, even the bones already formed must be affected. In this way the apposition of osteoid tissue as well as the increased resorption, admitted to occur, must be explained. The causal connection is at bottom as simple and plausible as is the old universally accepted experience that fractures occurring during pregnancy are slowly repaired because a proper callus is with difficulty formed. In the latter case there is a dearth of earthy salts for the apposition of new *pathologically conditioned* osseous substance, and it is but a step to the assumption that the *physiological* apposition also ceases when the lime-salts are appropriated to other purposes. It is possible too—at least in human osteomalacia—that derangements of digestion or resorption may co-operate, and thus interfere with the entrance of the salts into the blood. Some such cause must be assumed in those rare cases at least, where osteomalacia is observed in non-pregnant women or even in men, provided of course that some other disease has not in those cases been confounded with it.

So far as I am aware, there are no other pathological pro-

cesses in which the relative proportions of organic and inorganic materials are altered to the detriment of the latter. For the many diseases in which the bones become fragile or thin, or, as it is termed, worn away (*usurirt*), invariably involve at the spot affected the osseous tissue in *its entirety*. In this way atrophies of bone comparable to the senile osteomalacia may indeed arise ; but *actual degenerations* can never so originate. Yet even when we have succeeded in thus establishing the influence of an inadequate supply of lime on the nutrition of the tissues, the greater part of our task still remains to be accomplished. For a deficiency of lime-salts is much less commonly met with than is the opposite nutritive disturbance, in which the relative proportions of the organic and inorganic constituents are altered *to the detriment of the former*. True, the increase cannot well concern the inorganic materials dissolved in the juices or chemically united with the albumen of the tissues. An increase of the latter can hardly occur because chemical union presupposes a definite mutual relation of quantity, and the former is precluded by the simple fact that any augmentation would immediately be neutralised by increased excretion of the salts in question. No objection, however, can be raised *a priori* to the notion that undissolved salts are *mixed* with the constituents of the tissues in such a way that the intimate structure of the tissues remains unchanged, while their *ash contents* are considerably *increased*. By feeding amœbæ with cinnabar and then analysing them before excretion has occurred, mercury can be detected in their ashes, although there has certainly been no combination of their protoplasm with the cinnabar. There is an abundance of similar facts in human pathology. We need not again refer to *tattooing*, in which vermilion or Indian ink is introduced into the tissues and their juices by means of punctures. Much more striking examples are daily presented to us, in the absence of all wounds, by the lungs. For the common black pigment which often accumulates in astonishing quantities in the pulmonary tissues and bronchial glands is, as is well known, nothing but *finely divided carbon*, which, mixed with the air in the form of minute particles of soot, enters the alveoli during respiration. Some of the particles are here taken up by the epithelial cells, while

some pass free into the tissues of the alveolar septa and into the lymphatics. By what force they are conveyed into the interior of the septa has not yet been clearly made out, but when they have once entered the lymphatic stream the mode of their distribution through the pulmonary tissues and lymphatic glands is perfectly obvious. Their sojourn in the lymphatic channels is short, and after leaving them they occupy the tissues proper of the lymphatic glands and lungs. Here they remain an unlimited time, for the organism is unable to oxidise such mineral carbons. In precisely the same manner as this *anthracosis*, there is developed a *blue colouration* of the lungs in workmen engaged in working with ultramarine, a *siderosis* from inhalation of ferric oxide, and an accumulation of *flint-* and *limestone-dust* in the lungs and bronchial glands of stone-cutters and labourers in limestone quarries. The permanent or temporary character of these infiltrations is determined solely by the nature of the materials, *i. e.* it depends on whether they can or cannot be so altered by the organism as to become soluble and then excreted. While the inhaled flint-dust persists, the limestone dust—as shown by v. Ins in Langhan's laboratory—disappears in a comparatively short time, doubtless by transformation of the carbonate into bicarbonate of lime.*

But, however striking are the results of this inhalation of undissolved inorganic substances, the changes are always confined to the lungs and their lymphatic glands, and a deposition of the inhaled particles never occurs in any other locality. Hence the facts which have been collected with reference to the deposition of undissolved mineral substances in all possible tissues, when their absorption has taken place from the *intestines*, are still more remarkable. This applies above all to so-called *argyria*, *i. e.* the peculiar grey-blue discolouration acquired by the skin and by many of the internal organs after long continued internal administration of nitrate of silver. This affection depends, as has been deter-

* Traube, 'Deutsche Klinik,' 1860, Nos. 49, 50; Leuthold (Traube), 'Berl. kl. Wochenschr.,' 1866, No. 3; Koschlakoff, 'Virch. A.,' xxxv, p. 178; Virchow, ibid., p. 186; Knauff, ibid., xxxix, p. 442; Slavianski, ibid., xlviii, p. 326; Kussmaul, 'D. A. f. klin. Med.,' ii, p. 89; Zenker, ditto, p. 116; Merkel, Ziemssen's 'Hdb.,' i, p. 519; v. Ins., 'A. f. exp. Pathol.,' v, p. 169.

mined by a number of careful investigations,* on the *deposition of minute granules of silver* throughout the different organs, partly in the walls of the small vessels and partly in the connective-tissue, *e.g.* of the skin and the intestinal mucous membrane. The metal is also met with in the membrana propria of some gland-tubes, like the sweat-glands and renal tubules. Up to the present, however, no one has succeeded in discovering the laws governing the deposit of the silver in the various tissues, some of which, like the epithelia and central nervous system, appear invariably to remain free. Nor has the nature of the entire process been fully cleared up as yet. According to some writers the silver is resorbed as an albuminate, and having arrived in the various tissues with the transudation, is in them reduced. Others, while admitting that it thus undergoes resorption, believe that it is at once reduced within the intestinal wall, and deposited in the form of most minute granules beneath the epithelium of the intestines, whence it is gradually transported into the other tissues and organs. The latter view is, I willingly admit, in many respects seductive; but it must be borne in mind that the deposition of minutely divided vermilion or finely pulverised Indian ink, introduced directly into the blood of animals, does not take place in the localities which are the seats of the silver-deposit in argyria.†

The deposition of foreign mineral substances occasionally taken into the body cannot compare in importance with the analogous processes in which the inorganic materials forming constant and regular constituents of the food and therefore of the body are concerned. It is, indeed, inconceivable that the highly soluble alkaline salts should ever become deposited in a solid form. But the possibility of such an occurrence must all the more readily be acknowledged for the *earths*, whose basic salts are so difficult to dissolve in watery fluids that the means whereby they are kept in solution in the blood, lymph, &c., is still the subject of dispute. *Calcifica-*

* Frommann, 'Virch. A.,' xvii, p. 135; Huet, 'Journ. de l'anat. et de l. phys.,' iv, p. 408; Charcot and Ball, 'Dictionn. encyclop. de sciences méd.,' T. vi; Riemer, 'A. d. Hlk.,' xvi, pp. 296, 385; Neumann, 'Wien. med. Jahrb.,' 1877, p. 369; Weichselbaum, 'Wien. allg. med. Ztg.,' 1878, No. 15; J. Jacoby, 'A. f. exper. Path.,' viii, p. 198.

† Ponfick, 'Virch. A.,' xlviii, p. 1.

tion is in fact one of the commonest nutritive disturbances met with in the human body.* We speak of *calcification* when undissolved lime-salts are present in a tissue, but without having entered into such close combination with the organic substance of the tissue as is the case with bone. The earthy salts in calcification are simply mixed with the tissues; the latter are *impregnated* with them, just as with silver in argyria. The salts themselves are naturally the same as those composing by far the greater part of the inorganic material of bone, namely, calcium phosphate ($Ca_3 2PO_4$), with, usually, much smaller quantities of calcium carbonate, and, as a rule, traces of phosphate and carbonate of magnesia. No other nutritive disturbance is so easily and certainly recognised as calcification; for since precipitated earthy salts are concerned in it, the slightest vestige of them at once becomes apparent on microscopic examination, in the form of fine highly refracting granules which are completely dissolved by acids. If the calcareous particles are numerous, the affected part presents even to the naked eye a *whitish colouration*; and when the accumulation is still greater the spot is distinguishable to the finger by its *hardness*. But even when calcification is most extreme there is no uniform permeation of the tissues with lime-salts, such as is characteristic of bone. The earthy salts long retain their distinctly granular form; and at most the granules coalesce to form coarser, angular, very sharp-contoured grains; the formation of a really large, coherent, glistening mass of lime-salts is a rare event. Even then the mass cannot be confounded with true bone, inasmuch as the characteristic bone-corpuscles and lamellæ, to say nothing of the medulla, are wanting. On dissolving the salts by means of acids the original structure of the tissues comes into view unaltered, especially in the less extreme degrees of calcification; and when this does not occur it may be taken for granted in most instances that the constitution of the part had undergone considerable alteration before calcification set in.

If we attempt to explain how and from what causes this incrustation with earthy salts arises, the idea obviously sug-

* Virchow, 'Verhdl. d. Berl. med. Ges.,' i, p. 253; 'Cellular-pathologie,' 4 Aufl., p. 451.

gesting itself is that it is due to *a precipitation of the lime-salts of tissues whose salts were previously kept in solution.* There is hardly a single tissue in whose ash one cannot detect the same earthy salts which compose the pathological incrustations. Were the matter so simple, the problem would resolve itself into the discovery of the cause of the precipitation of the salts; such, for example, as the disappearance of the solvent. But a moment's reflection will show the untenability of this view. For the ash-contents of the tissues that are richest in inorganic materials—excepting of course the bones and teeth—amount at most to from 1 to 2 per cent., and in many fall far short of 1 per cent. Take, on the other hand, an extremely calcified artery, a calcified trichina-capsule or exudation, and you find the mass of the earthy salts falling little short of that of the original tissue. Hence it follows beyond all doubt that *the earthy salts of calcification must be conveyed to the part and deposited in it.* Accordingly it is fitting that we should first answer the question, Whence do the lime-salts come? and then attempt to discover the cause of their precipitation and deposit in particular localities.

By this question it is of course not intended to throw doubt on the fact that all inorganic materials are in the last instance conveyed into the body with the food. To manufacture lime-salts is beyond the capacity of the organism. But in the bones it has always at command a very considerable *store* of these salts, and hence we must at least leave it open to suppose that calcification consists in the removal of earthy salts from the skeleton and their deposition elsewhere. Virchow* was the first to direct attention to the actual occurrence of such *metastatic calcifications,* for which he proposed the name of *lime-metastases.* In the bodies of individuals in whom a rapid disappearance and absorption of considerable quantities of osseous tissue has followed some morbid process, such as multiple caries, extensive cancer or sarcoma of bone, marked calcification has been repeatedly observed post mortem. What Virchow specially determined, as bearing on the causal connection, was the very unusual situation of the calcification, for it always involved parts of the lungs or digestive canal, and here the connective tissue of the affected

* Virchow, his 'Archiv,' viii, p. 103, ix, p. 618.

patches was so infiltrated with lime-salts that the entire felt like pumice-stone. But though I am ready to acknowledge the connection, its explanation is, in my opinion, far from adequate. Nor is the circumstance urged by Virchow, and willingly admitted by us, of much avail—namely, that the excretion of earthy salts with the urine was in many of these cases hindered by disease of the kidneys. For the result would at most be an overloading of the blood with lime-salts, beyond all doubt in solution, and their non-excretion is far from making it intelligible in what way the removal of the superfluous salts to *the localities above named* is effected. Did a mere precipitation of the salts from the *quasi* over-saturated solution take place, we should expect—passing over other objections—that the deposit would then be found on the inner surface of the vessel walls, or at most in the walls, while *de facto* it is the mucous and submucous connective tissue and the pulmonary stroma, but not the vessels, that are calcified in these cases. We are compelled, so far as I see, to adopt the hypothesis that *special conditions,* determining the precipitation, exist in the affected localities—a subject which will more closely occupy our attention in dealing with the other varieties of calcification.

For when I counted calcification, or, as it is also termed, *petrification,* amongst the most common derangements of nutrition, I was not thinking of the lime-metastases; I had chiefly in mind the extreme frequency, I might almost say constancy, with which calcification sets in in *advanced life.* It is not, it is true, exclusively an attribute of old age. Opportunity not infrequently offers for observing it in early life or even in childhood; and that the age of the part is not an essential condition of its occurrence is most strikingly taught by the calcifications met with in the fœtal tissues of the placenta. Yet if we fix our attention more closely on the incrusted or petrified spots, it is at once apparent that they are by no means those in which an active vital metabolism prevails. A chief contingent is formed by *dead* masses retained in the body, such as parasites, like trichinæ, pentastomata, cysticerci; an extra-uterine fœtus, an old thrombus; or an old inspissated caseous exudation or purulent deposit. The dead trichina or cysticercus becomes infiltrated with

earthy salts from without inwards; the extra-uterine fœtus acquires an actual shell and is thus changed to a *lithopædion ;* the thrombus is transformed into a venous calculus; the exudation into a mortar-like concretion. Necrosis is, however, clearly unnecessary; *i. e.* complete extinction of the nutritive processes need not take place in order that a favourable nidus may be supplied for the deposition of earthy salts. It is enough that the vital processes be *considerably enfeebled and their energy greatly reduced.* You would hardly be inclined to look upon a trichina-capsule containing a living animal as altogether dead, and yet it regularly undergoes calcification in the course of a few years. When lime-salts are deposited in tendons, cicatrices, and pleuritic adhesions we have to do with instances of very slight metabolism and not with necrosis. To an *obsolescence* of this kind, as Virchow terms it, the frequently observed calcification of ganglion-cells is also beyond doubt attributable. Similar calcifications of the placenta, as well as the very voluminous ones occurring in tumours of low vascularity, more especially fibromas and myomas, must be referred to the same cause, although complete necrosis may possibly have a share in their production.

But what is it that determines the deposition of the lime-salts in precisely those localities where there is little or no metabolism? Precipitation of the earthy phosphates of the urine with the formation of a sediment in the bladder or the pelvis of the kidney, or even incrustation of the *epithelium of the open collecting tubes* in the renal pyramids is, we know, sufficiently explained by the lessened acidity or the alkalinity of the urine in such cases. But the conditions giving rise to a precipitation of earthy salts from the transudations are unfortunately altogether unknown to us, simply because we are ignorant as to the form in which they circulate in the transudations, *i. e.* of the means whereby they are held in solution.* As regards free pre-existent earthy phosphates, the carbonic acid contained in the fluid would be of essential interest. But since, according to the unanimous opinion of all more recent writers, at least a great part of the calcium phosphate unites with albumen to form an albu-

* Kühne, 'Physiol. Chemie,' 1868, pp. 153, 182; Pribram, 'Arb. aus d. Leipz. phys. Anst.,' 1871; Fokker, 'Pflüg. A.,' vii, p. 274.

minate of calcium, the relations here existing must be of a much more complex kind. It is quite possible, as Litten* is inclined to believe, that as the result of a change in the chemical constitution of the albuminous substances associated with their death or obsolescence, the lime-salts become arrested in localities where such change occurs. It is also possible that a retardation of the flow of the juices to and in the localities may play an important part in the deposition of earthy salts. At any rate it is only prudent to be slow in setting up a theory of the causes of the precipitation of earthy salts in necrotic and obsolescent tissues, since a single new fact may perhaps overthrow it.

But whatever be the reason of the calcareous deposit in particular localities, the facts themselves appear to be sufficient explanation of the *calcification* occurring *in old age.* This is chiefly characterised by the implication principally of the *circulatory apparatus,* which sometimes becomes the seat of a calcification whose extent and intensity are simply astonishing. On account of the remarkable bulk of the calcareous deposits, Virchow was long ago led to suspect† that they are perhaps closely connected with senile atrophy of bone, and constitute a variety of lime-metastases. This suspicion is, moreover, apparently strengthened by an interesting observation of Küttner,‡ who watched the development of an extreme calcification of most of the arteries of middle and smaller calibre in a youth of nineteen with caries of the dorsal vertebræ. Nevertheless, I cannot regard such a view as justified for the senile calcification of vessels. The postulate just laid down with regard to the seat of the metastatic calcareous deposit appears to be satisfied in Küttner's case; for the author states expressly that the masses were seated *on* and in the tissues of the intima, while the media and adventitia were completely free from incrustation. In senile calcification of arteries the condition is a very different one. Here the earthy salts are deposited in the muscle-fibres of the media, and partly, it is true, in the intima; but the deposition in the intima occurs, not in its innermost layers

* Litten, 'Virch. A.,' lxxxiii, p. 508.
† Virchow, his 'Archiv,' viii, p. 113.
‡ Küttner, 'Virch. A.,' lv, p. 521.

next the lumen of the vessel, but chiefly in the outer portions of this membrane. We are accordingly face to face with the same difficulty as in the other so-called lime-metastases; and Virchow's idea is still more incompatible with the fact that an extensive calcification of the vessels very often coincides with a non-atrophic condition of the osseous system. But when senile osteomalacia does coexist with calcification of the arteries, we might perhaps be equally justified in asking *a priori* whether the atrophy and softening of the bones are not due to the *precipitation in the walls of the arteries of the earthy salts* normally intended for the repair of the osseous tissue?

But if the lime-salts are not derived from the skeleton, they must be introduced into the body with the food, and the extent to which they are deposited in the vascular system of the aged is, on this view, all the more astonishing. Why, it may fairly be asked, are the walls of the vessels selected for the deposition of earthy salts? That this is not to be explained by a mere precipitation from the circulating blood upon and in the walls I have already intimated, and if the salts are only thrown down from the transudation of the vasa vasorum, it may be pertinently asked—Why is not the precipitation universal instead of being confined to the vessels? And why should the arteries alone be implicated, while the veins either escape altogether or are, in extremely rare instances, only very slightly affected? The last-mentioned circumstance—the freedom of the veins from senile calcification—has naturally long attracted the attention of pathologists, and by many of them has been referred to *the different quality of the blood in the two kinds of vessels*—a very obvious hypothesis. The view seems to be supported by the fact that incrustation of the valves of the left heart with lime-salts is extremely common, while a similar affection on the right side is very rare, as well as by the tendency of the renal glomeruli, which also contain arterial blood, to become coated with earthy salts. The difference in the carbonic acid contents of arterial and venous blood has by many writers been made answerable for the dissimilar behaviour of the two kinds of vessels towards the earthy salts. It is argued that since the carbonic acid tension is undoubtedly greater in the venous

than in the arterial wall, the earthy phosphates are held in solution in the former while they are precipitated in the latter. Yet, even neglecting the fact that the difference of carbonic acid tension in both kinds of vessels is by no means great, the argument is applicable only to the freely circulating earthy salts, and not to the albuminate of calcium, with which we have, you are aware, principally to reckon. But further discussion of the theory is unnecessary, since, though at first sight a plausible one, its untenableness is in my opinion clearly proved by *the invariable absence of calcification* from that vascular area, the carbonic acid tension of which is lower than elsewhere, namely, *the pulmonary veins.*

Under these circumstances we are driven to seek the cause of the almost exclusive preference for the arteries, not in the condition of the vascular contents, but in that of the vessel walls themselves. May not the arteries be subject to changes analogous to those which are met with in calcification of other organs, *i. e.* a considerably reduced metabolism and obsolescence of the tissues? As a matter of fact, the valves of the left heart and the arteries possessing vasa vasorum are in addition the seats of election *for the chronic inflammatory processes of the vascular system*; and everyone knows how the shrinking and thickening of the left cardiac valves, as well as arterio-sclerosis—*endarteritis deformans* of pathological anatomists—are extremely prone to become complicated by calcification. But this is not all; for it is invariably in the thickened portions of the intima, the so-called *semi-cartilaginous plates,* that the lime-salts are first deposited; and, conformably to the development of the callosities and formation of atheromatous patches, the calcification of the intima always proceeds from without inwards—a fact which, to my mind, affords very cogent evidence for a deposition of the lime-salts from the transudation of the vasa vasorum. In the veins and pulmonary arteries there are found at most mere indications of a process analogous to the sclerosis of the systemic arteries; but where, as may happen in exceptional instances, the thickening of the intima in both kinds of vessels is marked, deposition of lime-salts very quickly follows. That the factor so often dwelt upon—the cessation or great diminution of the metabolism—really plays a determining part in

the semi-cartilaginous plaques and other thickenings of arterio-sclerosis, may be accurately shown by microscopical examination. For, as Weigert* has pointed out incidentally, and Wardwell has convinced himself by a lengthy series of investigations carried out in the institute here, there is always present in the middle of a sclerotic area, a small or larger portion *without nuclei*, where the tissues have succumbed to *coagulation-necrosis*. Thus, the remarkable implication of the arterial system in senile calcification may in great measure be explained by the fact that endarteritic and atheromatous changes—in short, arterio-sclerosis—become more common and embrace larger tracts of the vessels as age advances. As for petrification of the media, and more especially of the muscle-fibres, we shall not be acting too boldly if we refer it also to an enfeeblement, or if I may so say, an exhaustion of vital energy, the parallel of the considerable reduction of elasticity consequent upon old age. At any rate, the media of the arteries in old persons always contains a smaller or larger number of muscle-fibres without nuclei and in a condition of coagulation-necrosis. No doubt the perpetual alternation of relaxation and constriction, as well as the very great internal pressure to which the arterial walls are exposed, play a part in all these changes, as shown by the fact that the points of origin and bifurcation of arteries are the earliest seats of sclerosis and calcification. A more thorough understanding of this connection is at present impossible. Should, however, any of you object to my deductions on the ground that *calcification occurs in the glomeruli,* which possess neither *vasa vasorum* nor muscle-fibres, I reply that with them the case is very different. For the earthy salts deposited on the vascular loops of Bowman's capsule have not been thrown down from ordinary transudations but from the urine, and are therefore perfectly parallel to the lime-infarcts of the pyramids or the lime-incrustations of the epithelium of the convoluted tubes. Precipitation occurs because the urine has not been able to keep the salts in solution owing to its want of acidity. When, indeed, the lime-salts remain in those portions of the kidneys in which they have been precipitated and incrust them,

* Weigert, 'Virch. A.,' lxxix, p. 113.

it is, in my opinion, simply because the glomeruli in question are partly atrophied, the urinary tubules shrunken and their epithelium necrotic—because, in short, a more or less extensive senile atrophy has taken place in the kidneys; and this is indicated, as a rule, by a certain amount of granulation of the surface of these organs.

In our discussion so far, we have paid no attention, as you have probably noticed, to a tissue occupying a very prominent place in the history of senile calcification, namely *cartilage.* Why do the cartilages of old people so regularly undergo calcification? Inflammations of cartilaginous tissue proper do not occur; and one would hardly be disposed to refer the calcification to an essential diminution of the metabolism, inasmuch as the tissue is non-vascular, and its metabolism at no time a particularly active one. Atrophic processes do, it is true, occur in the cartilages of the aged. *Fibrillation* or *asbestos-like degeneration,* accompanied by a certain amount of shrinking and dryness, is a very common occurrence, and is almost always found *e. g.* in the costal cartilages of old persons. But speculation as to the causes of senile calcification of cartilage is idle, inasmuch as *the petrification is never permanent like that of the arteries.* Rather the precipitation of earthy salts in cartilage is without exception a *provisional process;* and in old age, no less than during growth, is nothing but a preliminary to true ossification. For what reason this relation has been so frequently misunderstood, I do not know, but you may be absolutely certain that when in dividing the costal cartilages you come upon an obstacle resisting the knife, or when the thyroid cartilage breaks instead of bending, you have before you *genuine spongy bone provided with medulla,* and not a substitution of calcified for hyaline cartilage. The situation and amount of the spongy bone may be very different in different cases. If the ossification is very marked, as is not uncommon in the larynx, the entire cartilage is replaced by bone. In the costal cartilages we find either a peripheral shell of bone or a central bony core of larger or smaller size. The situation and amount of the osseous tissue depend, as in normal development, on the direction in which, and the activity *with which, the blood-vessels grow into the cartilage from the perichondrium.*

Since, then, the senile alteration of cartilage now under discussion is not due to a petrification, but to an *ossification,* the process has no analogy with calcification of arteries, and is on the contrary directly related to the normal, physiological growth of bone. For, as you are aware, almost the entire skeleton is originally preformed in cartilage; and it is only during the course of embryonic and extra-uterine development that a gradual substitution of bone occurs. In the end, only those portions retain their cartilaginous character which are termed in consequence *permanent cartilages;* those, namely, of the ribs, larynx, trachea, bronchi, and articulations. The means whereby these cartilages escape ossification are at present unknown; we can only say with certainty that their exceptional position is connected with the functions they have to perform. I have no fear that you will misunderstand me when I tell you that it is at any rate a very wise provision of nature that the permanent cartilages should be endowed with the capacity for opposing the penetration of the vessels as long as their nutrition and condition continue normal. At least you see what I am aiming at. If the nutrition of the cartilage must be perfectly preserved in order that penetration of the vessels may be guarded against, then *everything which unfavorably influences nutrition must bring with it the danger of ossification.* The old experience of surgeons and experimental pathologists that ossification commonly sets in during repair of a fracture or other wound of the permanent cartilages in man and animals is to be explained in this way; as are also the circumscribed ossifications of those parts of the respiratory cartilages, in the immediate neighbourhood of which an inflammatory or ulcerative process has become established, *e. g.* ossification of the arytenoid and cricoid cartilages in tubercular ulceration of the vocal cords.* What in young persons results from a wound or circulatory disturbance, is in old age the effect of senile fibrillation and atrophy. The vessels grow into the atrophic cartilage, convey the lime-salts into it, and open up lacunæ in the manner so well known; and since osteoblasts and marrow-cells are now produced, there is, in fact, a substitution of typical osseous tissue, with a regular marrow, for the original carti-

* Virchow, his 'Archiv,' iv, p. 297.

lage. These cartilages are therefore by no means so permanent as their name implies. They have simply preserved their youthful state for an extremely long period, but at last they, like the other cartilaginous portions of the skeleton, succumb to their regular fate, namely, ossification. The fact that the *articular cartilages* are wont to continue cartilaginous on into the most advanced old age does not in the least militate against this view. For, while they also succumb to an atrophy, often very marked in extent, and though atrophy is an indispensable preliminary to ossification as it in a sense opens up the way for it, the *vessels* are the real determining factor in the entire process, and *their penetration is rendered impossible* by the permanent pressure which the contiguous articular surfaces exert on each other at every movement. You will see how probable is this explanation on recollecting that some of the synovial vessels of the knee-joint which have developed in embryonic life are caused to atrophy and disappear by the regular friction of the articular surfaces after birth. Moreover, the comparatively frequent occurrence of bony ankylosis in old people proves clearly enough that, if the joints once become fixed from pathological causes, ossification of the articular cartilages, also, does not fail to set in in the aged.

Having, in senile ossification of cartilage, become acquainted with a process which is usually, but incorrectly, classed with the calcifications, we may be permitted to devote a few words to another pathological occurrence, which, though it likewise has no connection with calcification, is still undeniably related to the metabolism of the earthy salts, namely, the formation of *calcareous concrements* or *calculi*. I have already stated that a portion of these originate in an *actual incrustation with earthy salts*. Such are phleboliths, calcified thrombi, calculi of the lungs; the latter being incrustations of inspissated purulent masses contained in bronchiectatic dilatations or other cavities in the lungs. As regards the lime concretions in the *urinary passages* or in the preputial sac (in extreme phimosis), I need not again tell you where the cause of the precipitation of the earthy salts from the urine is to be sought for. The lime-salts also participate in the forma-

tion of gall-stones; for an insoluble or slightly soluble combination of biliary colouring matter with the lime dissolved in the bile forms the nucleus of by far the greater number of these calculi. A very special interest has of late been acquired by the concretions met with in the cavity of the mouth and its appendages, odontoliths, salivary calculi, and the stones occurring in the crypts of the tonsils, inasmuch as these are all attributable to bacterial action. This was first proved for the salivary calculi and dental tartar by Maas and Waldeyer,* and for the tonsillar stones by Klebs,† in all of which microscopic examination showed an organic basis consisting of dense colonies of bacteria, remaining after the earthy salts were dissolved. Klebs, who has carefully studied the nature of this mycosis, looks upon the bacteria concerned in it as identical with Remak's leptothrix buccalis, and believes that the leptothrix has the power of separating out the lime from all its combinations, and of assimilating it, or excreting it in the form of carbonate of calcium after the manner of the marine algæ. By far the greater portion of the lime appropriated by the leptothrix is derived from the earthy phosphates and from the bicarbonates of the solid and liquid foods or of the saliva, but the dentine is also drawn upon, when the enamel presents defects or fissures. The so-called *caries*, moreover, is, as shown by Leber and Rottenstein,‡ a destructive process originating solely in a growth of *leptothrix.* Wherever the leptothrix masses penetrate into the dental tubuli the dentine is first decalcified and softened, and then completely disintegrated. We, however, know no more of the chemical process whereby the leptothrix masses bring about this decalcification than of the chemical events occurring in bone-resorption by myeloplaques.

We have already thoroughly discussed the influence of calcification of the cardiac valves and of the arteries on the circulation. As to the import of the other calcifications it is

* Maas u. Waldeyer, 'Tagbl. d. Rostock. Naturforsch-Vers.,' 1872; cf. also Zahn, 'Virch. A.,' lxii, p. 560.

† Klebs, 'A. f. exper. Path.,' v, p. 350.

‡ Leber u. Rottenstein, 'Untersuchungen über d. Caries d. Zahne,' Berlin, 1867.

hardly possible to say anything of a generally applicable character; whatever can be said is already implied in their etiology. For if, as may be proved in the great majority of cases, the incrustation with earthy salts involves obsolescent or even necrotic parts, this implies that the calcified portions are *functionally as good as worthless* to the organism. Whether or not the calcareous concrements give rise to morbid phenomena will naturally depend on their size and situation.*

* On the subject of this chapter consult further Virchow, 'Cellularpathologie,' 4 Aufl., pp. 451, 503; the text-books of physiological chemistry of Kühne, Gorup-Besanez, Hoppe-Seyler, Voit, &c.; Beneke, 'Grundlinien d. Pathologie d. Stoffwechsels,' Berlin, 1874; Wagner, 'Hdb.,' p. 435; Perls, i, p. 194.

CHAPTER IV.

LIPOMATOSIS AND FATTY DEGENERATION.

Chemical identity of all the fat in the body.—Origin of the physiological fat.—Fattening and fatty atrophy.—Fatty infiltration and degeneration.—Inadequacy of morphological criteria.—Chemical differences.

Obesity.—Fat-production in the cartilages of children and in rapidly growing tumours.—Accumulation of fat due to deficiency of oxygen from pathological causes.—In the anæmic and phthisical or in other forms of cachexia as well as in old age.—Situation of the fat.

Fat-production from chronic alcoholism and as the result of elevated temperature.—Phosphorismus acutus.—Acute atrophy of the liver.—Acute fatty degeneration in the new-born.

Local fatty atrophies in consequence of interference with the supply of arterial blood.—The fatty kidney of mechanical congestion, cirrhosis of the liver, Bright's kidney, cholera kidney, &c.—Fatty changes in paralysed muscles.—Fatty involution of the uterus.—Production of fat in tumours of low vascularity, in old exudations, and in foreign bodies contained in the abdominal cavity of living animals.

Fatty changes in the nervous system.

Significance of abnormal fat-production.

Cholesterin.

Of the morbid derangements to which the metabolism of the organic tissue constituents is liable, none can compare in point of frequency with the abnormal appearance of fat. Particular organs and tissues, the liver, the kidneys, and next to these the heart and the vessels, are its favourite

seats, yet it is no exaggeration to say that in every tissue, though normally containing no free undissolved fat, smaller or larger fat-drops are occasionally met with. But is this really a morbid appearance? Are we not accustomed to look upon a certain abundance of fat as a trustworthy criterion of well-being and vigorous health? This is perfectly true, and the circumstance that an accumulation of fat may take place in the same tissue and locality under the most different conditions has long excited the interest of thoughtful pathologists. In the cells of the costal cartilages of little children, during the most active period of growth, it is usual to meet with a few large fat-drops, which are in all respects identical with those filling the cartilage-cells of the same region in old people. The liver of the phthisical not uncommonly contains as great an accumulation of fat as does that of the drunkard or glutton; and while the flesh of the best-fed cattle and swine is regularly interlarded with fat, the most marked phase of this condition occurs in the various forms of extreme muscular atrophy. To dispel any doubts on this point, I may say at once that *no chemical differences exist between these fatty changes, however heterogeneous in their nature.* Wherever fat is met with, and whatever the cause of its appearance, it invariably consists of a mixture of the three well-known glycerides, *tripalmitin*, *tristearin*, and *triolein.* To this extent our task is simplified; but, on the other hand, this very identity has the effect of enhancing the apparently paradoxical character of the fatty changes. Let us see if, by availing ourselves of physiological data, we can succeed in solving this problem.

Leaving out of account the fat dissolved in the fluids and tissues of the body, this substance occurs normally as droplets in the proper adipose tissue of the subcutaneous panniculus, the mesentery, the mediastinum, the fatty capsule of the kidney, &c.; it is further met with in the medulla of bone, in the sebaceous glands, in the mammary gland during lactation; and lastly it is very common in the liver. With regard to the source of the fatty material, it is now known for certain, after much discussion, that it is in part *the fat supplied as such in the food.* The mode and form in which it is absorbed and circulates in the blood are, you are doubtless

aware, still under discussion,* and the means whereby the organism effects the removal of the absorbed fat into the fat cells are involved in still greater uncertainty. Still the imperfection of our knowledge does not in the least detract from the fact that the fats consumed with the food can be, and are very commonly, deposited in the body. From the investigations of Radziejewski, Voit, Hoffmann, and others,† we also know enough of the conditions and details of this apposition of fat to enable us to identify the localities above mentioned as the depôts in which the fat of the food is stored up. At any rate the passage of the latter into the cells of the adipose tissue proper, of the bone medulla, of the liver, as well as into the milk has been determined in such a manner as apparently to satisfy the most exacting demands. But it is no less certain that the organism puts on fat when none is supplied in the food, *i. e. it has the power of manufacturing fat.*‡ The carbohydrates were long supposed to be the source of the manufactured fat, but this idea, you are aware, has lost ground, and it is now extremely improbable that fat is ever formed from them. Meanwhile it has become more and more certain that it can originate from *albumen,* on separation of a group of atoms containing nitrogen. With the evidence for this view you are already familiar from physiology, and we can the better afford to dispense with a recapitulation of it in this place, as you will shortly make the acquaintance of a number of pathological data which are thoroughly calculated to support the assumption. We are not sufficiently informed as to the organs in which the separation of fat from albumen occurs. That the cells of the mammary and sebaceous glands possess this power is beyond question, but the results of pathological experience, to which reference has just been made, render it questionable whether

* Kühne, 'Phys. Chemie,' p. 371; Röhrig, 'Arb. aus d. Leipz. phys. Anst.,' 1874; Zawilski, ibid., 1876, p. 147; Hensen, 'Pflüg. A.,' x. p. 111; Gad, 'A. f. Phys.,' 1878, p. 181; J. Munk, 'Virch. A.,' lxxx, p. 10; Will, 'Pflüg. A.,' xx, p. 255; Cash, 'A. f. Phys.,' 1880, p. 323.

† Radziejewski, 'Virch. A.,' xliii, p. 68, lvi, p. 211; Voit, 'Zeitschr. f. Biol.,' v, pp. 79, 329; Pettenkofer und Voit, ibid., v, p. 369; Hoffmann, ibid., viii, p. 153; Forster, ibid., xii, p. 448.

‡ Kühne, l. c.; Subbotin, 'Zeitschr. f. Biol.,' vi, p. 73; Pettenkofer und Voit, ibid., vii, p. 433; Forster, l. c.

the capacity is at all confined to certain organs, and is not rather an attribute of the cells of most tissues. Two circumstances especially increase the difficulty of coming to a decision on this question: even the fat derived from albumen may not have originated at the spot where it is discovered; while the absence of fat from certain cells in a normal condition by no means implies that no fat is there separated.

For in order that fat, whatever its source, may remain as such in the body, it is necessary *that it should not be further decomposed.* Though we are ignorant of the details of the transformations to which fat is subjected in the organism, there is no reason to doubt that the process is essentially an oxidation, whereby the substance, after passing probably through a number of intermediate stages, is finally converted into carbonic acid and water. But for this oxygen is required; and it is a very ancient experience that all conditions which facilitate the interchange of gases in the blood are obstacles to the apposition of fat, while opposite conditions are favorable to it. Men and animals who undergo much muscular exertion never become fat, and the cattle breeder keeps the animal he wishes to fatten as much as possible at rest. The favorable influence of a diet rich in carbohydrates on the accumulation of fat depends upon the fact that the oxygen unites in the first instance, and by preference, with the readily decomposable carbohydrates, so that what is left is insufficient for the oxidation of the fat. In a word, fat persists as such when *a disproportion exists between fat-production and fat-oxidation to the disadvantage of the latter;* and, naturally, this disproportion ensues on relative deficiency of disposable oxygen. That it is here quite immaterial whether the fat is supplied as such with the food, or has originated in the body through the decomposition of albumen, I have already indicated—a fact obviously implied in the identity of all the fat met with in the organism. Yet the rule would lose none of its force, even if we took into account the cases in which, after artificial feeding, a foreign fat is deposited in the tissues.

On attending to these considerations, you at once perceive that fat may make its appearance in the body under diametrically opposite conditions. It is increased, firstly, by a

very good and abundant diet. When the food consumed by an individual is more than sufficient to maintain, as Voit says, his albumen and fat in a stable condition, if he consumes superfluous fat or superfluous albumen, he will *of necessity put on fat,* provided there be no corresponding increase in the supply of oxygen. The cause on which the inadequate supply of oxygen depends is a matter of no importance, and want of muscular exercise or the consumption of large quantities of carbohydrates may play the same part here as any pathological factor that diminishes the absorption of oxygen by the blood. Moreover, an abundant supply of fat itself appears, according to Voit, to have the effect of diminishing the absorption of oxygen. In such circumstances—which are purposely brought about in fattening animals—the condition of all the organs and tissues continues excellent, while at the same time fat accumulates in the body. On the other hand, imperfect oxidation may, or rather must, also be followed by fatty deposition when the absorbed albumen is insufficient to repair the waste, *when, consequently, the albuminous contents of the body are diminished.* Here also it is in principle immaterial whether the unoxidised and therefore definitive fat is introduced as such with the food or is derived from albumen. For the result is in both cases the same: the fat of the body increases while its albumen diminishes; or, in other words, the *fat increases at the cost of the albumen.* The source whence the former is derived is of importance only *as it affects the locality of the fatty deposition.*

With regard to the question, where, in what parts of the organism, the fat is deposited, I have stated that the portion supplied with the food is always conveyed to the depôts so often mentioned—the adipose tissue, the bone-medulla, the mammary glands, and the liver—in which it accumulates till required or is at once used up in the production of milk and bile. We know nothing of the mechanism by which the deposition of the fat in the cells of adipose tissue, &c., is effected. It may be that the transudation and absorption by the cells are rendered possible by special properties of the vessels,* or, what is more probable *per se,* that the cells them-

* Toldt, 'Wien. akad. Stzgsb.,' 1870, lxii, Abth. 2, p. 445; Flemming, 'A. f. mikr. Anat.,' vii, pp. 32, 328.

selves possess peculiar powers; or perhaps cells and vessels are both endowed with a special capacity. The predisposition of the above-named localities to fatty deposition, depending on certain unknown peculiarities, is best shown by the fact that the fat derived from superfluous albumen also accumulates in these reservoirs. In fattened animals and in corpulent persons, whatever may have been the nature of their food, the fat is found only in these situations. Moreover, it has been proved in a special series of experiments* that the fat of milk as well as that of the cellular tissue and bone-marrow is produced and stored up in precisely the same manner, whether the fodder contains fat or only albumen and carbohydrates. Manifestly, this is possible only if the fat, on being separated from albumen in the cells of the various tissues and not immediately oxidised, is transported from the spot where it is produced to the reservoirs. Such transport certainly occurs in over-production of fat, or, as it is shortly called, lipomatosis. But what happens when the albumen contents of the body decrease simultaneously with the production of fat, when the latter is formed at the expense of albumen? Is the fat then stored up in the depôts? In so far as it is derived from the food—yes; for it is not possible to imagine how in these circumstances any change in the laws regulating the circulation of fat should result. But the fat originating from the albumen of the tissues, when the albuminous waste is not sufficiently repaired, need not necessarily be removed to the reservoirs. In this case it is easily conceivable that, owing to the enfeeblement of the flow of lymph which invariably occurs here, the separated fat may remain a long time lying, almost as if it were meant to take the place of the absent albumen in building up the cell. As a matter of fact, there are many important data in pathology going to show that this is actually the case, and at any rate this, to my mind, very plausible assumption is excellently calculated to elucidate so-called *fatty atrophy, i.e.* a fatty change having atrophic characters.

For on this assumption the occurrence of fat in localities and tissue-cells *where it is not normally met with* becomes at once intelligible. The separation of fat from albumen is, as

* Subbotin, 'Med. Ctbl.,' 1866, p. 337; Forster, l. c.

already hinted, a very general process, and may perhaps take place in the great majority of cells, at least when albuminous in their nature. Ordinarily we see nothing of the separated fat, because it always immediately undergoes further oxidation; and when by reason of an inadequate supply of oxygen it is not consumed, we find no trace of it in the cells, provided the decomposed is replaced by fresh albumen; the fat is then carried off to the depôts. When, on the other hand, the loss is not made good, the fat is wont to remain in the cells in question. But its sojourn hardly becomes permanent; it must not be forgotten that whenever the supply of oxygen is adequate thereto oxidation will occur, and that even when the fat is not oxidised, its transport to the depôts will nevertheless take place in the end, though only tardily and gradually. Still, the fat in fatty atrophy remains much longer in the cells in which it has originated than is ever the case in excessive production or lipomatosis; so that the chances of occasionally meeting with the former in the various organs are much greater.

In saying this we have at the same time hit upon a circumstance which enhances the difficulty of understanding the abnormal fatty infiltrations and degenerations to an incomparably greater extent than was the case with the calcifications; namely their *unstable*, or if I may say so, *fluctuating* character. Were the destiny of the fat always so definitely marked out into the phases above described, the matter would be simple enough. For we could then feel certain that all the fat met with in adipose tissue, bone-marrow, the mammary and sebaceous glands, should be placed under the head of lipomatosis, being either derived as fat from the food or from surplus albumen by decomposition. Similarly the fat occurring in the epithelium of the lungs and kidneys, in the muscles, cartilages, walls of the blood-vessels, &c., would be referred to fatty atrophy. In the liver at most we should have to admit the possible existence of both varieties. Now I mentioned a moment ago that the fat of fatty atrophy is also ultimately removed to the legitimate storehouses, so that fat which is not derived from the splitting up of superfluous albumen may also be deposited *e. g.* in the subcutaneous and intermuscular connective tissues. Still greater com-

plications arise from an opposite direction. In the view above expounded it was implicitly assumed that the fat of lipomatosis, produced by the decomposition of cell-albumen, is either *at once* consumed, or, when oxygen is deficient, *at once* removed in the juices to the fat-reservoirs. Such an assumption, however, is scarcely reconcilable with the nature of all the coincident events. At least it must be admitted that the separate stages of the process may not always follow one another so promptly, and that an interval, however short, may elapse between the separation of the fat and its consumption or removal. Should we examine the organ or tissue in this intermediate stage we might very easily fall into the error of supposing that we had before us a case of fat-production from deficient supply of albumen, *i. e.* a case of fatty atrophy—a mistake which could not have arisen had the individual lived a little longer.

Since there is here such imminent danger of fundamental error, you will not be surprised that the want of definite criteria which would afford a clue to the nature of any accumulation of fat should long have been felt. The most ready plan was to seek for morphological diagnostic characters ; and pathologists by taking two evident and undoubted contrasts, the panniculus adiposus of well-nourished individuals and true fatty heart, came to regard the presence of *large fat-globules* as supplying the criterion for the fat of lipomatosis, or, as it is called, *fatty infiltration*, and to look upon the occurrence of *fine droplets* as diagnostic of *fatty atrophy* or *degeneration*. Now the distinction most decidedly holds good of the localities selected ; the large oil-globules of the panniculus are undoubtedly due to infiltration, and the same may be said of those in the mesentery, the fat-capsule of the kidney, and the bone-marrow. On the other hand, the fine droplets filling the muscle-fibres of the heart and in extreme cases completely obscuring their cross-striping, are as certainly the product of an atrophic process, and exactly resemble the fat-droplets in the epithelium of Bright's kidney. Yet it would be a serious mistake to generalise these experiences into an universally applicable law. Anyone who has examined an intestine during the process of fat-resorption knows that the epithelium is filled with minute droplets of oil ; but here, if

anywhere, we have to deal with a true *fatty infiltration.* Moreover, the finely granular fat so commonly found in the epithelium of the straight urinary tubules in dogs and cats is most certainly owing to resorption from the urine, *i. e.* to true infiltration. Still more notable are the exceptions when the fat takes the form of large globules. These globules are beautifully seen in the liver after phosphorus poisoning, although no one can doubt the degenerative character of the fat-production. The cells of the respiratory cartilages of old persons contain very large oil-droplets, and the fat deposited in the connective tissue of an extremely atrophied muscle is indistinguishable by the naked eye or microscope from that of the best-developed panniculus, although the signs of its atrophic origin are abundantly evident on the face of it. In truth, *a morphological distinction of this kind is absolutely untenable.* When fat appears as an undissolved substance, it first invariably takes the form of minute droplets and granules, which are distinguished by the well-known reactions. When it has increased a little in amount, these finest granules unite to form small drops with a high refractive index; and it altogether depends, if I may so say, on the molecular structure of the cells whether the small drops, if there are several of them, coalesce to form large ones. In the cells of the adipose and lax cellular tissues, of the bone-marrow, the liver, and the cartilage, large oil-drops are always formed when a sufficient quantity of fat has accumulated; while in smooth and striped muscle-fibre, in the epithelium of the kidneys, the lungs, cancerous tumours, as well as in the endothelium of the vessels, &c., a coalescence of finer droplets, however numerous they may be, never takes place. In the sebaceous and mammary glands drops of all sizes may be present.

Moreover, on remembering the origin of abnormal fat, and bearing in mind that the whole of the fat met with in the cells of all the organs, excluding the fat-depôts proper, is formed on the spot from albumen and has escaped oxidation and removal, you will hardly expect that marked morphological differences in the condition of the fat will indicate whether the decomposed albumen of the cells has been replaced or not. Rather we might anticipate some measure of

success from a chemical examination of the whole of the affected organ. For *in fatty atrophy the percentage relation of the fat to the remaining solid constituents must of necessity prove much higher than in accumulation of infiltrated fat in the organ.* An examination of different fatty livers, which Perls* carried out with this object in view, gave a result perfectly satisfactory, and quite in harmony with the foregoing presupposition. Yet a useful result can, obviously, only attend such examination when the other tissues have become very subordinate in amount to the fattily degenerated elements, and in organs where there is no true fatty tissue; the method is useless, *e. g.* in the heart and in cartilage. Add to this the amount of detail and labour involved, and you will certainly prefer physiological to chemical analysis in attempting to decide on any given case. It will be advisable then to subject the facts supplied by pathologico-anatomical experience as to the presence of abnormal fat in the body to examination from the standpoint now attained by us.

Assuming our view to be correct, it must be possible to discover in the first place *why the fat is not consumed,* and in the second place we must be able to decide in individual cases whether we are dealing with superfluous infiltrated fat or with fatty atrophy; we have, in other words, to determine *whether the fat,* in so far as it is not contained in the special reservoirs, *occupies a cell with normal or with diminished albuminous contents.* The ultimate cause of the persistence or non-oxidation of fat is, I need hardly repeat, *an inadequate supply of oxygen.* Now the intensity of the oxygen stream is determined in a normal condition solely by the amount of oxygen consumed in the various kinds of work done by the organism,* so that when the elements of the organs require much oxygen for the discharge of their functions, much will be taken up; while if their requirements are less, a less quantity will suffice. Thus there is nothing pathological in the circumstance that a well-nourished individual leading a sedentary life does not absorb enough oxygen to consume all the fat supplied directly with the food, or derived by decompo-

* Perls, 'Med. Ctbl.,' 1873, p. 801; Lehrbuch, i, p. 170.

† Pflüger, his 'A.,' vi, p. 43.

sition from its albumen, especially if the oxygen at the same time meets with easily decomposable matters, like the carbohydrates. No one would think of supposing a person enjoying a certain *embonpoint* to be therefore diseased, any more than a fat ox or sheep would be so regarded. And yet the transition from this to what is called *obesity* is but a gradual one, and the latter condition has always been looked on as anything but enviable both by the laity and by physicians. By obesity is to be understood an accumulation of fat considerably in excess of the normal standard, which first occurs in the legitimate localities, namely the panniculus adiposus, the mesentery and mediastinum, the omentum, around the kidneys, and on the pericardium, but which, in extreme cases, also invades the inter-muscular connective tissue and the submucous and subserous connective tissue of the intestine, being then accompanied as a rule by a large fatty liver. If we attempt to explain the origin of obesity, it is obvious that here also the fat is either introduced as such with the food, or is derived from the splitting up of albumen, and—since individuals with pure polysarcia usually possess perfectly and powerfully developed organs—from the superfluous albumen of the food. As there is at least no reason to suppose that obese persons can produce fat from any but the legitimate materials, we may unhesitatingly lay down the rule that such individuals would put on no fat, were it not that their consumption of fatty and albuminous food is out of proportion to the oxygen at their disposal. Anything of a problematical character in this rule disappears on considering that obesity is markedly a hereditary disease, which often attacks every member of a family, and which, though usually not appearing till after the age of twenty or even later, occasionally affects even children. Similarly there are among domestic animals certain breeds which, it is well known, are especially adapted for fattening.* In all these cases there must evidently be a special *predisposition*, in virtue of which fat is deposited in circumstances where in

* Roloff, "Die Fettdegeneration bei jungen Schweinen." 'Annal. d. Landwirthsch,' 1865, discussed in 'Virch. A.,' xxxiii, p. 553; 'Die Schwindsucht, fettige Degeneration, Scrophulose und Tuberkulose bei Schweinen,' Berlin, 1875.

the ordinary healthy man or animal it would be oxidised. True, it is difficult to say on what this predisposition depends. It is certainly not due to interference with the supply of oxygen to the blood of the pulmonary capillaries, as the result perhaps, of disease of the respiratory organs, for obese persons are usually furnished with excellent lungs, and any pulmonary disease that may occur is rather secondary to the polysarcia. Nor do we gain anything by adopting Toldt's view,* that the adipose tissue is to be regarded as a specific organ and to be sharply distinguished from ordinary connective tissue; its function being to take up fat just as the renal epithelium takes up urea. For even on the assumption that this specific apparatus is from the first unusually developed in the obese, we should be no nearer a knowledge of the source of the large quantity of fat filling the cells of the apparatus. So far as I see, we have no alternative but to assume that *the oxidation of fat is abnormally reduced* in the individuals now under discussion. Is the quantity of hæmoglobin contained in their blood-corpuscles less, and the capacity of the latter to unite with oxygen by consequence diminished? Or is there a reduction in the energy with which the oxidative process in the tissue-cells takes place? I personally look upon the latter as the more probable explanation; at least, I am unable to see any ground against assuming such differences in the functional power of the cells. The popular distinction between the *phlegmatic* and the *sanguine* temperaments is not without its justification, and though the very much greater predisposition of the former to *embonpoint* is in great part attributable to their manner of living, above all, to inequality between their bodily movements and those of the sanguine, yet everyone knows the spare individual in whom, despite his sedentary life, a most ample diet leads to no accumulation of fat. Nor can the increased fat-production in human beings or animals after castration be explained on the theory simply that the albumen which would otherwise have been appropriated to the formation of semen or ova, or used up in menstruation, now constitutes a source of fat. We must rather assume an alteration of the entire constitution in such persons, manifesting itself by a

* Toldt, 'Wien. akad. Stzgsb.,' 1870, lxii, Abth. 2, p. 445.

reduced energy of the oxidative process in the tissue-cells. For the blame must assuredly be laid on the cellular elements of the different organs. *In the cells, and as the result of their action,* there is effected a union of oxygen with fat, either supplied as such or separated from albumen; the function of the cells is therefore defective when the fat is not consumed in a normal manner. The promptness, moreover, with which in the obese fat is carried off to the well-known reservoirs proves that there is no diminution or slowing in the juice-stream of such persons. Not till the polysarcia is extreme does the latter appear to suffer, and then the non-oxidised fat continues long in the cells in which it is separated, and is not only found in the situations formerly mentioned, but the fibres of the heart and voluntary muscles, the epithelium of the kidneys and other organs are filled with minute fat-droplets,—an appearance which may at least be explained in this way, although, as I willingly grant, it admits of another interpretation.

If then in obesity we have fatty accumulation by reason of inadequate oxidation, both of fat from the food and fat derived in the body from albumen, it is evident that every organ. in which fat is normally separated may participate therein It is thus intelligible, also, why the accumulation is not confined in these cases to the usual localities, but goes on to implicate lax connective tissues like the intermuscular, which generally remain free. For when such considerable quantities enter the juice-stream, it is only to be expected that a portion at least will be deposited in closest proximity to its place of origin or separation; and for the fat separated in the muscles the nearest repository is of course the inter-muscular cellular tissue. Nor is there any difficulty in explaining the storage of fat in the liver of the obese. For this organ is one of the physiological fat-depots, and when an abundance of emulsified fat begins to circulate in the juices, and hence in the blood, a large amount will necessarily be taken up by the hepatic cells. Whether this fat is derived from the food or from the splitting up of albumen is altogether immaterial; and it is even doubtful whether the fat which regularly collects in the liver (especially in sucking animals) after consumption of large quantities of milk is

directly conveyed from the intestine to the liver by the portal vein. The fact that in the liver fat not only collects, but is predisposed to remain a long time is, for one thing, connected with the supply to the hepatic cells of *blood distinguished by its poverty in oxygen*—even the blood conveyed to the liver by the hepatic artery has become venous before discharging itself into the hepatic capillaries. In the second place there are, as you know, many facts going to show that the fat of the hepatic cells is utilised for the production of bile, perhaps to form the *cholalic acid.* It is therefore open to suppose that the biliary function of the hepatic cells in the obese may be enfeebled and impaired, just as is the oxidative function of various other cells. As a matter of fact, the belief that very fat persons produce little bile has been widely prevalent among physicians in all ages.*

In no circumstances has polysarcia anything in common with the *atrophic* processes. On the contrary, the metabolism of the remaining constituents of the body, more especially the nitrogenous, is usually very active, as evidenced by the large quantity of urea excreted in the urine of such persons. The condition involves no more than a disparity between fat-consumption and fat-production, permanent in the obese, and transitory in the liver of sucking animals and children. Still less related, if possible, to atrophy is the fat so commonly observed in the cartilage-cells of children and young animals. This fat is, in my opinion, nothing but a secondary product of the very energetic metabolism. For it occurs, as we have said, at an age when growth is most rapid, and it is precisely in the best-nourished individuals that the most numerous and largest oil-droplets are found. Who can doubt that, owing to the continuous new formation of tissue, the supply of material is here very active; and we shall hardly err if we regard this cartilage-fat as simply indicating that fat-consumption has lagged behind the more energetic fat-separation. How greatly this delay is favored by the abundance of carbohydrates in the milk taken by children, and by their comparative bodily inactivity, is at once apparent. A welcome confirmation of this view is in my opinion afforded by the fact that fatty accumulation in the

* Frerichs, 'Klinik der Leberkrankheiten,' 2 Aufl., i, p. 292.

cells is very commonly met with not only in *rapid physiological growth* but in *pathological* formations as well. In rapidly growing enchondromata, carcinomata, sarcomata, and all other kinds of *tumours* it is extremely common to find the cells filled with more or less numerous fat-droplets.

In the cases of fatty change hitherto discussed there is, it is evident, nothing essentially pathological; since, by adopting a suitable diet and mode of living, even the obese have completely at their disposal the means of confining their fatty deposition within physiological bounds. Much greater pathological interest attaches therefore to a number of fatty affections which are due to altogether abnormal influences, and which cannot, at any rate, be prevented or removed by physiological regulative measures. The ultimate determining factor in all these cases is, of course, the insufficient supply of oxygen to the tissues; and if we ask how this scarcity may be conditioned, the thought first suggesting itself is—by some *respiratory derangement*. If the access of atmospheric oxygen to the pulmonary capillaries is impeded owing to stenosis or obstruction of the air-passages, or if a portion, more or less considerable, of the respiratory surface becomes lost to respiration through destruction or blocking of capillaries, the result must, it is argued, invariably be a diminution in the amount of oxygen taken up by the blood. The correctness of this reasoning appears to be fully supported by the frequent occurrence of fatty liver and other fatty changes in the phthisical. To the existence of such a connection, however, the objection has fairly been raised that fatty liver is absent in analogous diseases of the respiratory apparatus, *e.g.* in emphysema and the chronic bronchitis associated with kyphosis. If you consider, moreover, the means at the disposal of the organism for compensating the constriction of the air-passages or the decrease of the pulmonary vascular area—how it has recourse in the former case to dyspnœic respiration, and in the latter to acceleration of the flow through the vessels still remaining—you will no doubt perceive that the supply of oxygen to the tissues cannot well, as the result of such affections, fall below the necessary quantum, provided the strength of the affected individuals continues unimpaired. More weight attaches in this

respect to those alterations of the blood which involve a considerable reduction of its hæmoglobin-contents, *e. g. leukæmia, chlorosis,* and all true *anæmias,* whether due to a single or to repeated hæmorrhages or originating as an idiopathic affection like *progressive pernicious anæmia.* In fact, I have already (vol. i, p. 493) dwelt on the never-failing presence of fatty change in each and all of these affections, and stated that it is even one of the pathognomonic peculiarities of the more severe forms of anæmia. Of course, we must not think of the connection so directly, or, if I may say so, so roughly as to imagine that the absorption of oxygen is reduced in precisely the same degree as are the hæmoglobin contents of the blood. By the experiments of Bauer,* and still more tellingly by those of D. Finkler,† it has been proved that no immediate alteration in the absorption of oxygen follows the abstraction of even considerable quantities of blood from a healthy animal, and that twelve, twenty-four, or more hours must elapse before the absorption of oxygen and excretion of carbonic acid are reduced—provided at least that the condition of the animal remains in other respects the same. Here, however, we have an important reservation. Strong and healthy animals move about briskly and actively, those in whom anæmia is established remain quietly sitting, or lie perfectly still, through an instinctive desire to avoid everything that would increase their need for oxygen. In addition, the functional power of the organs and of their cells is undoubtedly impaired by the loss of blood, and will remain so till the blood-mass has been restored by regeneration. But if the heart, respiratory muscles, glands, &c., work with less energy than before, they will consume a smaller quantity of oxygen, and the supply to the blood and tissues will be correspondingly maintained *within abnormally low limits.* If the connection be looked at in this way, there will be found nothing contradictory in the circumstance that chlorosis and especially leukæmia—diseases in which the hæmoglobin contents of the blood sink to an extremely low value (cf. vol. i, p. 478)—are not accompanied by such intense and widespread fatty changes as are the true anæmias. There is,

* Bauer, 'Zeitschr. f. Biol.,' viii, p. 567.

† D. Finkler, 'Pflüg. A.,' x, p. 368; Pflüger, ibid., x, p. 251.

however, a still better test of the correctness of our view. For if it be really the reduced functional power, the feebleness of the working organs, that determines the falling off in the absorption of oxygen, this falling off must be no less marked in all the remaining forms of cachexia. Now it has long been known with regard to *aged persons* that their consumption of oxygen is very much reduced ; and although respiratory measurements have not, so far as I am aware, been carried out as yet in cases of *carcinoma, chronic dysentery,* and *intestinal phthisis,* &c., still pathological anatomy is of service in repairing this deficiency. At any rate, it appears to me that *the great frequency of fatty changes in all such chronic affections* cannot, bearing in mind our previous conclusions, be interpreted except on the above assumption.

It is to this general *cachexia,* which must necessarily appear in the course of chronic pulmonary phthisis with its hæmoptysis, purulent expectoration, diarrhœa, night-sweats, and above all hectic fever, that the fatty liver of the phthisical is due, while the emphysematous, whose nutrition and strength remain comparatively speaking unaffected, are protected from this as well as from other fatty changes. The situation of the latter is in all these cases approximately the same. After the liver—which for reasons already stated is the favourite seat of fat-accumulation—the heart and diaphragm are chiefly affected ; next to these come the walls of the blood-vessels, all their coats being involved ; and lastly the kidneys, the accumulation in which occurs chiefly in the convoluted but also in the straight tubules. Occasionally, however, the fat is much more widely distributed, and senile fatty change especially may involve every organ, genitals as well as lens, the cornea, cartilage, and all the epithelia. The bone-marrow of the aged is remarkable for its richness in fat. These, you perceive, are only in part the same localities as become involved in obesity, and by no means the physiological fat-reservoirs alone. On the contrary, in many of these cases, more especially the phthisical, the panniculus adiposus and omental and mesenteric fat are reduced to an extreme degree, and sometimes completely absorbed ; and this contrast between the wasting taking place in the physiological depôts and the fatty changes occurring elsewhere has led to some of the

most singular hypotheses.* These are not necessary, if the subject be regarded in a strictly objective manner. The fat, in the fatty heart of the anæmic, cachectic, or aged, occupies not the intermuscular connective tissue, but the muscle-fibres themselves, and their cross-striping may in consequence be completely concealed or obliterated. In the same way it fills the epithelium of the urinary tubules and the cells of the cornea within the limits of the arcus senilis, as well as the muscle-fibres of the media and the endothelium and intima-cells of the vessels. Its origin in all these places is evident without discussion : *it is separated from the albumen of the respective cells.* Since we also know that there is not sufficient oxygen to consume the fat, the only question to be answered is—whether or not the decomposed albumen is *replaced, i. e.* whether we have here to do with fatty infiltration or with fatty atrophy. On considering that these fatty changes occur in anæmic and cachectic individuals, you can hardly doubt which alternative should be adopted. *They are true fatty atrophies, i. e.* the albuminous contents of the affected elements are diminished and partly replaced by fat, and, bearing in mind the (hypothetical) laws previously laid down, according to which the fat of fatty atrophy is not immediately removed to the reservoirs, its presence in the muscle-fibres, renal epithelium, &c., will appear quite natural. A reduction in the juice-stream is in these cases, if anywhere, comprehensible.

Nor is there any reason why we should not regard *the fatty liver of the cachectic* as an example of fatty atrophy. We should then have the fat separated from albumen in the hepatic cells, and remaining in them because it is neither burned nor used up in the production of bile. And this latter element would be of considerable importance, having regard to the mal-nutrition and deranged digestion of the individuals in question. Yet it cannot be denied that a portion of the fat in these cases may have been derived as such from the food and be simply stored up in the liver. At any rate, the condition of the other fat-reservoirs is quite in harmony with this notion. For in some of these cases, as *e. g.* pernicious anæmia and senile cachexia, true adipose tissue is

* Rindfleisch, 'Path. Gewebel,' § 63.

abundant enough. It is found in the aged in the bone-marrow at least, and in the panniculus, &c., of the anæmic. Wherever internal fatty changes are associated with extreme atrophy of the subcutaneous fat, as in the phthisical and very frequently the carcinomatous, the two alterations are far from being developed simultaneously; removal of the fat from the panniculus has invariably preceded the internal fatty changes. Wasting, disappearance of adipose tissue, is merely part of the general atrophy developed in consequence of the phthisical or cancerous disease; and not till the functional power of the working organs has suffered severely as a result of this general atrophy are the conditions necessary to reduced supply of oxygen, and hence to fatty degeneration, presented.

While the impairment of the process of oxidation, and the diminished supply of oxygen depend, in the fatty changes just discussed, on the general cachexia, *i. e.* are conditioned by the internal economy of the cells forming the tissues and organs, there is, in addition, a number of agents which are capable of directly impeding and diminishing the oxidative processes of the body. These agents differ greatly in character, and their mode of action is far from clear. First amongst them is *heat;* for it has recently been determined by several exact experiments* that animals absorb less oxygen and give off less carbonic acid, the higher the temperature of the surrounding medium. In the next place, it has long been known that the *use of alcohol* diminishes the excretion of carbonic acid and absorption of oxygen.† Further, according to the investigations of Bauer,‡ the falling off in the quantities of oxygen taken up and carbonic acid excreted is extremely marked in acute *phosphorus poisoning,* where it may amount to a reduction to almost half

* Litten, 'Virch. A.,' lxx, p. 10; Erler, 'Ueber das Verhältniss der Kohlensäureabgabe zum Wechsel der Körperwärme,' I.-D. Königsberg, 1875.

† Prout, 'Annal. of Philos.' (by T. Thomson), ii, p. 328, iv, p. 331; Lehmann, 'Lehr. d. phys. Chemie,' iii, p. 404; Perrin, 'Compt. rend.,' lix, p. 257.

‡ Bauer, 'Zeitschr. f. Biol.,' vii, p. 53; cf. Storch, 'Den acute Phosphorforgiftning,' Kopenhagen, 1866; Fraenkel u. Röhmann, 'Zeitschr. f. phys. Chemie,' iv, p. 439.

the normal values. One circumstance is specially calculated to intensify our interest in the action of these agents, namely, the simultaneous *increase in the disintegration of albumen,* which sets in at least under the influence of warmth and phosphorus, with the result that *while the excretion of carbonic acid falls, that of urea* (in birds, of *uric acid**) *rises.* This striking contrast is at any rate worthy of attention; it would indeed be of capital importance were it really the expression of a law which A. Fraenkel† is inclined to lay down on the strength of these very facts. According to him, *the disintegration of albumen in the body must increase with the reduction of the oxygen-supply.* Fraenkel has in fact brought forward some noteworthy evidence in support of this position. Dogs, which had been almost asphyxiated by narrowing of the trachea kept up for several hours together, invariably excreted more urea on the day of experiment than on the preceding and following ones—the diet being of course the same, or the dogs deprived of all food. After poisoning with carbonic oxide, he also determined an increase in the excretion of urea; and, in perfect accordance with these results, Bauer ‡ had already found that in animals, when after abstraction of a large quantity of blood the absorption of oxygen becomes reduced, the excretion of urea increases. Whether, indeed, these facts are sufficient to allow of the deduction from them of the above-mentioned law, is a point which I would leave for the present undecided, remembering how complicated are the metabolic processes of the organism. As regards alcohol, this agent is directly stated not only to check the excretion of carbonic acid but that of urea as well;§ and certainly the former effect is of subordinate importance in its bearing on the problem now occupying our attention.

For if alcohol lessens the energy of the oxidative processes, the corpulency of habitual drinkers might be ranked with obesity depending on constitutional causes. Here

* H. Meyer, 'Klebs' Arch.,' xiv, p. 313.

† A. Fraenkel, 'Virch. A.,' lxvii, p. 273.

‡ Bauer, 'Zeitschr. f. Biol.,' viii, p. 567.

§ Obernier, 'Pflüg. A.,' ii, p. 494; Fokker, 'Nederl. Tijdsch. v. Geneesk.,' 1871; Riess, 'Zeitschr. f. klin. Med.,' ii, p. 1.

there is no sort of difficulty. On the other hand, the fatty changes in acute *phosphorismus* were not intelligible till the extreme alterations in the metabolism had been discovered. If, under the influence of the phosphorus circulating in the juices, there is a considerable increase in the disintegration of albumen and a corresponding falling off in the absorption of oxygen, extensive fatty changes may be brought about independently of the supply of fat or albumen in the food; *for fat can and will be produced at the expense of the albumen of the tissue-elements.* Thus Bauer* did not poison the dog, the subject of his experiment, till the animal had lost the greater part of his fat through prolonged starvation; and yet there were developed, in the complete absence of food, fatty changes in the liver, heart, kidneys, blood-vessels, and voluntary muscles. In the institute at Breslau precisely similar results were obtained by us with starving guinea-pigs, which were kept for several days in an atmosphere of 36°—38° C. The emaciated animals exhibited the most beautiful fatty changes—in the liver, heart, kidneys, and voluntary muscles.† Moreover, as you are aware, an old and approved accessory in fattening animals, is the keeping of their stalls really warm, besides giving them suitable food and restricting their movements as far as possible.

Such being the state of affairs, we are involuntarily led to seek for a similar causal connection in the case of some other diseases characterised by extensive fatty changes, and to attribute these diseases also to *reduced absorption of oxygen with increased disintegration of albumen.* I have here in mind more especially the so-called *acute atrophy of the liver* and certain forms of *icterus gravis*—diseases in which the autopsy is well known to reveal a complete accordance with acute phosphorus poisoning as regards the hæmorrhages and fatty changes. Obviously, I do not mean that acute atrophy of the liver and acute phosphorismus are identical processes. Who could entertain such a view, remembering the disparity in the course of the two affections, even in point of time? But it is not impossible that there may be present in both analogous and kindred profound alterations of the

* Bauer, 'Zeitschr. f. Biol.,' vii, p. 53.

† Litten, 'Virch. A.,' lxx, p. 10.

metabolism, which would of course be followed by similar disturbances of the nutrition of the tissues and organs. The careful analyses of the urine, carried out by Schultzen and Riess,* on the strength of which these writers declare against the affinity of the two affections, appear to me to prove, both with regard to acute hepatic atrophy and acute phosphorismus, that it is the oxidative processes in the organism that are above all *impeded.* In hepatic atrophy the place of the gradually disappearing urea is taken in the urine by easily oxidisable nitrogenous and non-nitrogenous substances containing a large amount of carbon, such as leucin and tyrosin, sarcolactic acid, oxymandelic acid, and even peptonoid bodies. But in the severest, fatal cases of human phosphorus poisoning the urea of the urine also decreases towards the end, and makes way for substances that are more closely related to the earliest products of retrogressive metamorphosis.† You will not be sorry to dispense with hypotheses on the connection between destruction of the hepatic cells and this impairment of the processes of oxidation; enough that the fatty change, when regarded in this light, ceases to be a mere raw, incomprehensible fact. Our position is not much better as regards the so-called *acute fatty degeneration of the new-born*—an affection which frequently causes great destruction amongst lambs, young pigs, and foals;‡ and is, moreover, by no means so rare in new-born children as the scanty records§ contained in the literature might lead one to suppose. In most of the cases which I have had an opportunity of examining, I found a more or less extensive *atelectasis* of the lungs, besides fatty changes in the heart, respiratory muscles, liver, and kidneys; but who would venture to decide whether the former was not merely an effect of the cardiac and muscular fatty degenerations? For those cases where the fatty degeneration is present at birth we are obliged to have recourse to unknown disturbances of the intra-uterine metabolism.

* Schultzen and Riess, '(Alte) Charité-Annalen,' xv.

† Cf. A. Fraenkel, 'Berl. klin. Wochenschr.,' 1878, No. 19.

‡ Roloff, l. c.; Fürstenberg, 'Virch. A.,' xxix, p. 152.

§ Buhl, 'Bair. ärztl. Intelligenzbl.,' 1861, No. 45; Buhl and Hecker, 'Kl. d. Geburtsk.,' Leipzig, 1861, p. 296; Hecker, 'A. f. Gynäk.,' x, p. 537.

On reviewing the varieties of fatty change which have till now occupied our attention, you will notice that the causal and conditioning factors, wherever discoverable, were invariably such as affect the organism in its entirety. The changes themselves, accordingly, were generally disseminated, at least throughout all the tissues in which fat is separated physiologically. Localised fatty changes are, however, not only possible, but must of necessity occur wherever separated fat fails to be consumed through want of oxygen, or to be conveyed to other localities by reason of a too-feeble lymph-stream. The fatty infiltration of rapidly growing cartilage and of many tumours, already mentioned, is a striking example of local fatty change. Yet *localised fatty atrophy* is naturally much more frequent than this local *embonpoint*, as it may be called. The most certain and simple expedient for securing a local diminution of the oxygen-supply is, I need hardly say, *limitation of the arterial blood-stream* to the part in question; this however involves at the same time imperfect replacement of the albumen split up, and by consequence *atrophy*. Each and every agent by which an abnormal resistance can be interpolated in the arteries of a part may therefore be attended by fatty atrophy. As examples I may refer to the fatty degeneration of the cardiac musculature and of the kidneys in severe *sclerosis of the arteries;* of the liver and kidneys in extensive *amyloid degeneration* of the vessels; and of the same organs in constriction of the vessels through contracting connective tissue (*cirrhosis of the liver, contracted kidney*). A similar explanation applies to the fatty changes so often appearing in the train of *permanent venous stagnation,* as observed in the fatty nutmeg liver and the cyanotic fatty kidney of heart disease. And if the cells of inflamed organs very frequently succumb to fatty atrophy—I remind you of Bright's disease—this is due simply to the *inflammatory disturbance of the circulation, i. e.* to the inadequate supply of arterial blood, which must be especially marked in chronic inflammation, where the retardation of the flow outweighs the hyperæmia. This view perfectly harmonises with the fact that the epithelium of the kidneys very commonly undergoes fatty change after *an attack of cholera, i. e.* after it has for some time been supplied

by a minimal and certainly inadequate blood-stream. All these processes, however different in themselves, have one feature in common—interference with the afflux of arterial blood; but, let it be clearly understood, merely *interference with,* not *prevention of,* the supply. The latter, you are aware, is inevitably followed sooner or later by necrosis, while for the separation of fat from albumen, the action of living cells is necessary; the splitting up of albumen into fat and nitrogenous matters is *a function of animal cells.* We have sometimes an opportunity of observing this distinction in a highly demonstrative way. After ligaturing the renal artery on one side in the dog, smaller or larger areas of the kidney will still be supplied by the small anastomosing arteries of the capsule. On examining the organ some days afterwards, you will find that these areas have the epithelium of the urinary tubules fattily degenerated, while most of the remainder of the kidney is completely necrosed. Still more striking if possible are the cases where intense fatty change attacks the muscles after embolic or thrombotic occlusion of *single* arteries of the leg; while occlusion of all or of the principal arteries leads, as you know, to gangrene of the extremity.

If you consider further how intimate is the relation between work and blood-supply of an organ, more particularly a muscle, you will not be surprised to find that *inactive and paralysed muscles very frequently undergo fatty change.* In the horse, according to the statements of veterinarians,* it is quite a regular occurrence for fatty degeneration to supervene after a time in the muscles of a paralysed extremity. In the human subject also we often meet with an analogous condition of the muscles of the leg in *ankylosis of the knee* with the bones fixed at an acute angle, as well as in cases of *atrophic paralysis.* It is indeed a question whether the simple atrophy of the muscle-fibres in these diseases is not invariably preceded by fatty changes. If it be so, we should then have a most simple explanation of the fact that atrophy

* Roloff, 'Die Fettdegeneration bei jungen Schweinen, Annal d. Landwirthsch,' 1865, discussed in 'Virch. A.,' xxxiii, p. 553; 'Die Schwindsucht, fettige Degeneration, Scrophulose und Tuberkulose bei Schweinen,' Berlin, 1875.

of the muscle-fibres is so very often combined with an interstitial accumulation of fat, *i. e.* with the development of true adipose tissue between the muscle-fibres. This tissue would on this supposition be fat which had in the first instance been separated from a portion of the albumen of the muscle-fibres, and, after remaining in them for some time, had finally been transferred to the cells of the intermuscular connective tissue. The latter would then become fat-cells, and the muscle-fibres atrophy owing to defective repair.

The *fatty involution and atrophy of the uterus* after parturition is also readily explainable on the hypothesis of diminished arterial supply (cf. vol. ii, p. 610); and the same remark applies to the fatty changes so very frequent in all kinds of *tumours poor in vessels.* I do not now allude, I need hardly say, to the accumulation of fat in the cells of rapidly growing tumours, a matter to which reference has already been made. In such cases we have to do with superfluous fat originating in a very active metabolism and only temporarily stored up, while fatty atrophy occurs especially in very old and slowly growing tumours, the metabolism of which must be feeble owing to the paucity of vessels. The fatty atrophy, such as often takes place in myomata, carcinomata, sarcomata, &c., should rather be placed in the same category with the alterations to which inflammatory products and purulent exudations are regularly liable after remaining long in the same locality, or becoming encapsuled, or at least cut off from active interchange with the circulating blood. The white blood-corpuscles are not carriers or transporters of oxygen like the red; and since Ewald* proved that the oxygen-tension of purulent exudations is even less than that of venous blood, it is not surprising that the pus-corpuscles in an exudation should after a time so certainly succumb to fatty degeneration. The fatty changes in fish-lenses, testicles, in short, in all kinds of bodies† and dead parts introduced into the abdominal cavity of living animals, which at one time gave rise to so much discussion, are, we now know, to be referred to the *pus-corpuscles; these enter the foreign body and there*

* Ewald, 'A. f. Anat. u. Phys.,' 1873, p. 663, 1876, p. 422.

† Rud. Wagner, 'Göttinger Nachrichten,' 1851, No. 8; Burdach, 'Virch. A.,' vi, p. 103.

undergo fatty degeneration, as has been proved in a most convincing way by B. Heidenhain.* The chief interest of these results consists in their overthrowing for these cases also the doctrine of a direct transformation of dead albumen into fat; wherever fat is separated from albumen in the organism, the separation, as I have already emphatically stated, is effected only in and by the agency of living cells. For the rest, the ripening of Roquefort cheese and the formation of adipocire does not occur without the co-operation of living organisms.

We have in the last place to consider the fatty changes taking place in a tissue, no mention of which, you have probably noticed, has yet been made: I mean the nervous system. Fatty changes in the nervous system, though by no means rare, occupy a position peculiar to themselves. Not as though the appearance of fat were here *chemically* inexplicable! Far from it; for although food-fat cannot well enter these tissues, there is, on the one hand, no scarcity of albumen in them, while, on the other, a most abundant source of fat exists in the lecithin-bodies. But admitting the possibility, it is far from proved that fat is separated from the lecithin of the medullary sheath under conditions analogous to those in which it is derived from the albumen of muscle-fibre or renal epithelium. Were it really so separated, we must now and then be in a position to see nerve-fibres or ganglion-cells filled with fat-drops or droplets, precisely as in muscle-fibres, liver-cells, and the like. This, however, is never the case, not even in the ganglion-cells; though a fatty degeneration of these cells has often been described and even looked upon as the anatomical basis of certain cerebral diseases.† In examining encephalitic and myelitic patches the mistake has commonly been made of regarding large inflammatory corpuscles of somewhat striking form as ganglion-cells in a state of fatty degeneration;‡ and there is practically no evidence that the coarse granules sometimes met with in the

* B. Heidenhain, 'Ueber d. Verfettung fremder Körper in d. Bauchhöhle lebender Thiere,' I.-D. Breslau, 1872.

† Meschede, 'Virch. A.,' xxxiv, pp. 81, 249, lvi, p. 100.

‡ Popoff, 'Virch. A.,' lxiii, p. 421; Huguenin, 'A. f. Psych. u. Nervenkrankh.,' iii, p. 515; Jolly, 'Stud. aus. d. Inst. f. exp. Path. in Wien,' 1870, p. 38.

ganglion-cells in insanity are really fat-droplets. The same remark applies to the nerve-fibres. Kühne* long ago pointed out how uncertain it is that the highly refracting globular drops which make their appearance in a divided nerve-fibre are really fat; but even if this objection were wholly set aside, *the appearance of these drops is invariably preceded by the complete disintegration of the contents of the nerve-fibre, or at least of the medullary sheath.* Such being the case, the process can scarcely be likened to the fatty change in a muscle-fibre, the result of which, even in its most pronounced form, is at most the obscuring of the cross-striping. As a matter of fact, wherever unmistakable fat is met with in the nervous tissues, it occurs either as a perfectly amorphous, *emulsion-like, fatty detritus* (in patches of softening) or in the form of the much-discussed *inflammatory corpuscles.* The latter, I have already told you, are nothing but *colourless blood-corpuscles,* which have taken up disintegrated or dead nerve-substance and manufactured it into fat; in saying which I leave it quite undecided how many of the granules contained in the inflammatory corpuscles, and still more in the emulsion-like detritus, are actually fat and not rather lecithin or one of its derivatives. If this view be correct, neither fatty infiltration nor fatty atrophy occurs in the nervous system—no fatty change in our sense of the term. The appearance of fat in nervous tissue always involves the complete disintegration of functional elementary parts; and wherever inflammatory corpuscles are met with in the fully developed brain, cord, or peripheral nerves, it may be assumed unhesitatingly that a destruction of nerve-fibres (or cells) had taken place there. Let it be clearly understood, in the fully developed organ; for, as Jastrowitz† has shown, inflammatory corpuscles are *a normal constituent* of the developing central nervous system, not only during intra-uterine existence, but also for the first few months after birth. They are probably connected with the formation of the medullary sheaths. Whether the granules of these inflammatory corpuscles are really fatty in their nature is, it is true, undecided.

On the mode of manifestation, or *symptomatology, of fatty*

* Kühne, 'Phys. Chemie,' p. 354.

† Jastrowitz, 'A. f. Psych. u. Nervenkrankh.,' ii, p. 389, iii, p. 162.

change I have hardly anything to add to what has already been stated. Everyone knows that a part which contains much free undissolved fat looks *white* or *yellowish white*, and has a doughy, soft consistence. As regards the microscopical appearances, by far the most important point is the situation of the fat; whether the drops be large or small they invariably occupy the *cells* of an organ, or their equivalent elementary parts *e.g.* the muscle-fibres; they are never seated in the intercellular substance. To this rule there is no exception, and wherever an apparent one occurs, as *e. g.* in Bright's disease, the fat-droplets are found, not in the interstitial tissue, but exclusively in the *lymphatic vessels;* the fat is, so to say, surprised during removal. Fortunately this limitation of the fat to the tissue-cells is not a mere isolated fact that we have simply to record, but a necessary circumstance, as you will at once perceive on recalling to mind the mode of its origin in the organism.

According to our plan, we shall hold over the discussion of the importance of fatty change till we come to deal with the pathology of the organs individually. I have already dwelt on its most essential features so far as heart and vessels are concerned. Here I wish merely to warn you against overestimating the seriousness of fatty changes. There was a time when the latter constituted the true panacea of pathology, and was called upon in explanation of all possible kinds of functional disturbance—I may remind you, for example, of fatty alteration of the renal epithelium and albuminuria. Now-a-days we are more reserved, and with reason. It is perfectly true that the substitution of fat for part of the albumen of a cell or muscle-fibre involves a proportionate loss of working or contractile substance. But you know, in the first place, that the discovery of fat in a locality does not always mean the absence of albumen; and it is, in the second place, unquestionable that even fatty atrophy may be completely neutralised and effaced, on restoration of the normal metabolism, *i. e.* on the supply of a sufficiency of oxygen and renovation of the albumen. But when abnormal metabolic conditions persist, when especially the disintegration of albumen progresses, then indeed fatty atrophy is but the beginning of the end.

In concluding this chapter I may be allowed to say a few words on the presence in the body of *free undissolved cholesterin,* the appearance of which has undoubtedly a certain relation to fatty change. With respect to the nature of this relationship we can only say that wherever free cholesterin is met with, there are always present in addition fattily degenerated cells and free emulsion-like fat derived from the disintegration of the cells and suspended in the tissue-juices. Thus cholesterin is found as characteristic, thin, rhombic tablets, with notched angles, in the atheromatous patches of arteries, in ovarian cysts, in old encapsuled and caseated exudations, in atheromata and cholesteatomata, goitres, and so forth. The question how the cholesterin has arrived in these structures has lately been greatly simplified by the discovery that it is widely distributed throughout the animal organism, and is in particular a constituent of the red and colourless blood-corpuscles.* Nevertheless, we are still without any explanation as to the process by which the deposition of cholesterin in crystalline form is effected. The view that it is set free through fatty disintegration of cells containing cholesterin, or has originated in the locality as a product of some unknown decomposition is certainly much more probable than is the fabled cholesteræmia of some years past.† For whatever we may think of the importance of cholesterin to the organism, it is at least certain that in the localities in which it is deposited in crystalline form the existence of a vigorous metabolism is altogether out of the question.‡

* Benecke, 'Stud. über d. Verbreitung v. Gallenbestandtheilen im thier. u. pflanzl. Organismus,' Giessen, 1862; 'Grundlinien d. Path. d. Stoffwechsels,' 1874, p. 194; Kühne, 'Phys. Chemie;' Hoppe-Seyler, 'Med. chem. Unters.,' i, p. 140, 162; 'Pflüg. A.,' vii, p. 409.

† A. Flint fils, 'Recherches expér. sur une nouvelle fonction du foie,' Paris, 1868; Kol. Müller, 'A. f. exper. Path.,' i, p. 213; Krusenstern, 'Virch. A.,' lxv, p. 410.

‡ On the subject of this chapter consult Virchow, 'Cellularpathologie,' 4 Aufl., p. 400; 'Arch.,' i, p. 94; B. Reinhardt, ibid., p. 20; Wagner's 'Hdb.,' pp. 414, 542; Perls, 'Lehrbuch,' i, p. 158; cf. the published researches of the Munich physiologists, which have for the most part appeared in 'D. Ztschr. f. Biol.;' further, Kühne, 'Physiolog. Chemie,' p. 365, and the text-books of physiology and physiological chemistry by Foster, Hoppe-Seyler, Voit, and others.

CHAPTER V.

COLLOID AND MUCIN-METAMORPHOSIS. CLOUDY SWELLING. AMYLOID DEGENERATION. ABNORMAL PIGMENTATIONS.

Colloid and mucin-metamorphosis of goitres, colloid cancers, myxomata, and ovarian cystomata.

Cloudy swelling.

Waxy degeneration of muscles.

Amyloid degeneration.—Its local and progressive forms. Seat, distribution, and causes of the latter.—Pathogenesis. —Importance.

Amyloid of the prostate and nervous system.

Pigment-metamorphosis.—Melanæmia.—Melanotic tumours.—Icterus.—Pigmentation of atrophic adipose tissue and muscles.—Bronze skin.—Ochronosis.

We now come to a series of nutritive disturbances of the tissues, distinguished by the appearance of matters which do not occur in the physiological organism, and the dependence of which on abnormal chemical processes may consequently be regarded as certain. Owing to this their foreign character, these nutritive disturbances can usually be diagnosed as such without any difficulty; but when we inquire into their intimate nature and the conditions under which they originate the obscurity is proportionately great. The reason of this is mainly the imperfection of our knowledge of the *albuminous bodies*. For in all these derangements of nutrition we have to deal with certain changes in the condition of the albumen of the tissues, either of consistence or optical properties, reaction to acids or other agencies. On reflecting how little we know of the constitution of albumens, it will at once be clear to you that even an approximately accurate solution of the problem is not possible at present. In most cases we

cannot even determine whether we are dealing with independent substances or with a mixture of such.

This applies to the so-called *colloid,* by which term is understood a transparent, colourless, or pale yellowish substance of gelatinous consistence, appearing on microscopic examination almost completely homogeneous, or at most faintly granular. The typical seat of this colloid is the *thyroid gland ;* here it appears in the form of small lumps, which may coalesce to form large masses ; it is so found in all kinds of *goitre.* Chemically the colloid material is in part composed of unmistakable mucin, yet the great bulk of it undoubtedly consists of one or perhaps more albuminous bodies. Of these one appears nearly related to the alkali-albuminates, while another is insoluble in water and acetic acid,* owing possibly to its mixture with large quantities of sodium chloride. In microscopic and naked-eye appearances, the gelatinous material of *alveolar* or *colloid cancer* bears the closest resemblance to the colloid substance of the thyroid gland, yet chemical examination shows that its albuminoid constituents are completely outweighed by the *mucin.* Now, inasmuch as the gelatinous substance of colloid cancers fills the alveolar spaces, and so occupies the region which in ordinary cancers is taken up by the epithelium, we have here, certainly, the same process on which the mucous metamorphosis of genuine epithelium depends ; moreover, colloid cancer is found chiefly in organs, like the stomach and large intestine, where a mucin-metamorphosis of epithelium occurs physiologically. There is another group of tumours distinguished by their considerable mucin-contents, namely, the *myxomata.* The mucus of the myxomata is quite independent of epithelial production ; the tumours belong to the connective-tissue group, and no part of the mucin is contained in cells. The latter are embedded in a jelly-like, homogeneous, intercellular substance, and it is here the mucin is found. It cannot, then, have arisen by transformation of the albuminoid cell-protoplasm, and its source must be sought in collagen. All

* Virchow, his 'A.,' vi, p. 580 ; 'D. krankhaften Geschwülste,' Berlin, 1867, iii, p. 5 ; Eichwald, 'Verhdl. d. Würzb. phys. med. Ges.,' v., p. 270 ; 'Beitr. z. path. Chemie d. gewebsbildenden Substanzen,' 1873 ; Kühne, 'Phys. Chemie,' p. 415 ; Hoppe-Seyler, 'Phys. Chem.,' p. 721.

myomata have a more or less considerable collagen-contents, and develop by preference in a gelatine-yielding substratum. The *mucous softening* of the symphysial and intervertebral cartilages of old people may be included under the same head. On the other hand, the fluid of ovarian cystomata contains no mucin, although it may be very viscid and tenacious. Its mucous consistence is given it by peculiar albuminous-bodies, so-called *paralbumin* and *metalbumin*, which are not precipitated by boiling and a small quantity of acetic acid.* That the epithelium of the cyst takes an essential part in thus altering the ordinary transudation-albumen is self-evident, but the precise conditions of the process are as little known to us as are those of the mucin- and colloid metamorphoses.

Still more unsatisfactory, if possible, is our knowledge of *parenchymatous degeneration* or *cloudy swelling*, so called by Virchow.† Parts affected by it do not present post mortem that peculiar glossy, juicy condition characteristic of healthy organs; they are markedly dull and *opaque*, and even thin slices are not transparent; it is, to use Virchow's apt comparison, as though the organs had been *cooked*. On microscopic examination of such parts a certain *granular condition* of the cells is noticed, due to finer and coarser granules, which are not present, or not so numerous, in a normal condition. This is really the only change revealed by the microscopic examination; and you will therefore easily see that, in organs like the liver, the cells of which have normally a very granular protoplasm, the diagnosis of cloudy swelling can be more certainly made by the naked eye than by means of the microscope. Parenchymatous degeneration, besides involving the liver, is met with in the kidneys, where the convoluted tubules are its usual seat; further, in muscle-fibres, especially of the heart; lastly, in the parietal cells of the peptic glands. These, you observe, are the same organs which we saw are peculiarly liable to fatty change; and it becomes necessary, therefore, to determine in the first place

* Scheerer, 'Verhdl. d. Würzb. phys. med. Ges.,' ii, pp. 214, 278; Eichwald, l. c.; Haerlin, 'Chem. Ctbl.,' 1862, No. 56; Obolensky, 'Pflüg. A.,' iv, p. 346.

† Virchow, 'A.,' iv, p. 261, xiv, p. 35; 'Cellularpathol.,' 4 Aufl., p. 375.

whether the cloudy swelling does not simply represent the commencement of fat-metamorphosis. But the granules of parenchymatous degeneration are not dissolved by ether, and disappear in acids and alkalies; their other reactions also prove beyond doubt that they are not fatty but *albuminoid* in character. True, this albumen must differ from the normal albumen of the cell-protoplasm and transudations, for the optical change could not otherwise be easily understood. It is possible that a spontaneous solid precipitation or *coagulation* of a fluid albuminous body is at the bottom of the occurrence, but it is also possible that some other modification of the albuminous substances has taken place. The condition is certainly not due, as has been supposed, to simple rigor mortis; for, to say nothing of the fact that cloudy swelling must then appear in every dead body as a transitory phenomenon, muscular fibre in rigor mortis is not at all granular. Hence those persons too who lay much stress on the circumstance that the change under discussion has never yet been observed except in the dead body must admit unconditionally that the cell-substance in these cases had undergone some kind of alteration *intra vitam.*

Accordingly, it is not at present possible to state with any degree of accuracy the chemical characters of cloudy swelling, and we are equally far from a knowledge of the conditions on which it depends. Cloudy swelling is met with chiefly in *infective* diseases, typhus and typhoid, pyæmia and puerperal fever, smallpox, scarlet fever and erysipelas, severe diphtheria and glanders, also in cerebro-spinal meningitis; diseases of very different kinds which, save their infective character, have scarcely anything in common. Most of them are, it is true, markedly pyrexial, and this has suggested the idea that the cause of cloudy swelling should be sought in the elevated temperature.* Yet this idea appears to me hardly tenable in view of the fact that the condition is generally absent in some markedly pyrexial diseases, like *e. g.* uncomplicated pleuro-pneumonia, and, on the other hand, occurs in some apyrexial affections, as, for example, carbonic-oxide poisoning. If, then, pyrexia is at all influential in producing the condition it is so at most indirectly, perhaps by disturbing

* Liebermeister, 'D. A. f. kl. Med.,' i, pp. 268, 461.

the circulation, either by altering the quality of the blood or its movement, transudation, &c. We have no alternative but to refer the cloudy swelling to some such unknown disturbances; all the more so, as on such hypothesis there would be nothing extraordinary in the supervention under certain circumstances of fatty change. A coincidence of this kind cannot, of course, prevent us from distinguishing as clearly between the two derangements of nutrition as the chemical differences demand. In the one case we are dealing with fat, in the other with a modification of albumen. Both may be derived from the same albumen, but just as fatty change is not always preceded by cloudy swelling so cloudy swelling does not always terminate in fatty change; on the contrary, it may be regarded as certain that in the vast majority of cases of recovery the cloudy swelling simply recedes, giving place to normal albumen.

Why the various organs should in these general diseases be attacked so unequally by the cloudy swelling, the chief seat of the alteration being at one time the heart, at another the liver, at a third the kidneys, remains till now altogether inexplicable. On the view just stated it is, on the other hand, easy to understand its *local* development as the result of severe circulatory disturbance. Thus severe inflammation of any of the foregoing organs usually leads to a more or less pronounced parenchymatous degeneration of its cellular elements.

While we were obliged to leave it doubtful whether cloudy swelling consists in the abnormal coagulation of a fluid albuminous body, we may confidently affirm this of the so-called *waxy degeneration of muscles*.* To the naked eye the affected muscle appears paler than normal, and varies in colour from reddish grey to whitish grey, *resembling the flesh of fish*. On microscopic examination there is found, instead of the typical cross-striping, a faintly glistening substance in the form of irregular lumps and fragments inside the sarcolemma.

* Zenker, 'Ueber d. Veränd. d. willkürl. Muskeln im Typh. abdom.,' 1864; Erb, 'Virch. A.,' xliii, p. 108; Martini, 'D. A. f. kl. Med.,' iv, p. 505; Hoffmann, 'Virch. A.,' xl, p. 505; Neumann, 'A. d. Heilk.,' ix, p. 364; Cohnheim, 'Embol. Processe,' Berlin, 1872, p. 34; Weihl, 'Virch. A.,' lxi, p. 253, containing also numerous references to the literature of waxy degeneration of muscles; Strahl, 'A. f. exper. Path.,' xiii, p. 14.

This alteration takes place in *all* muscle-fibres when wounded, torn, or crushed, whether the injury be inflicted in the living individual or after death, but before the setting in of rigor mortis ; it is here simply *a form of coagulation interfered with and rendered irregular by the trauma.* But in addition certain changes, the nature of which is unknown, take place in the contractile substance of muscles which have long been paralysed, and also in the adductors, abdominal muscles, diaphragm, &c., under the influence of certain diseases, especially typhoid. As a result the contents of the muscle-fibres do not become rigid as usual, but are transformed into the waxy, glittering masses just described, with the cross-striping completely obliterated. Whether this striking change in optical properties is due simply to the unusually *speedy* occurrence of coagulation of the myosin with subsequent contraction of the coagulum, as Martini claims, or to saturation with lymph of the fibre which has already perished *intra vitam ;* or whether again peculiar molecular or chemical alterations of the muscle-fibre are at the bottom of it, I shall not venture to decide. So much, however, is certain—that in the entire process of waxy change we are dealing, not with a pathological process, but solely with a characteristic post-mortem appearance. Whether it sets in after the death, or during the life, of the individual, in particular muscles or muscle-fibres, the occurrence of waxy degeneration is always preceded by loss of excitability, death, of the fibres.

Contrasting with the foregoing is another condition, also termed *waxy* or *lardaceous,* but for which the usual name is *amyloid degeneration ;** for this may unhesitatingly be said to be the most important of all the albuminous degenerations. A tissue thus altered contains a peculiar, waxy, glistening substance of pretty considerable consistence and great resisting power towards chemical and physiological agencies of all sorts, *e. g.* the gastric juice. This material is further characterised by its colour-reactions ; iodine stains it reddish brown or brown violet ; iodine and sulphuric acid, iodine and chloride

* Rokitansky, 'Lehrb. d. pathol. Anat.,' 1846, i, p. 445, 1855, i, p. 326, iii, p. 276 ; H. Meckel, '(Alte) Charité-Annal.,' iv, p. 264, 1853 ; Virchow, his 'A.,' vi, pp. 268, 416, viii, pp. 140, 364, xi, p. 188, xiv, p. 187, xv, p. 332 ; 'Wurzb. Verhdl.,' vii, p. 222 ; 'Cellularpath.,' p. 432.

of zinc, or iodine and chloride of calcium, render it dark blue, green, or bluish green. Another colour-reaction, distinguished for its extreme delicacy, has recently been discovered; methyl-violet (iodine-violet, gentian-violet, Leonhardi's ink) stains amyloid substance a beautiful and brilliant red, while ordinary cell-protoplasm, &c., assumes under its action an intense blue colour.* In passing, I may say that to me the methyl-reaction appears to possess unmistakable advantages over the iodine, not, indeed, for naked-eye purposes, but in microscopical examinations. Not only is the colour-contrast sharper and therefore less likely to give rise to error, but the reaction is, I think, a more sensitive one. This is to be inferred at least from the fact that we have repeatedly obtained very evident methyl-staining in tissues where the iodine-reaction gave no certain result. The behaviour of the substance towards iodine, and iodine with sulphuric acid, has, in addition to its diagnostic value, a very special interest, inasmuch as this reaction was the cause of its being ranked partly with cholesterin and partly with the carbohydrates. Virchow, to whom we are indebted for the most exact information on the degeneration now under discussion, for a long time actually called the material *animal cellulose*, and the name still retained in ordinary use, "amyloid," originated in the same idea. Meanwhile Kekulé† in the first instance, and more accurately Kühne and Rudneff,‡ have shown by chemical analysis that amyloid substance has nothing in common with the carbohydrates, but is, on the contrary, a *nitrogenous body* with a percentage composition *the same as that of the albumens.* Amyloid is indeed sufficiently distinguished from the other albuminous bodies occurring in the animal organism by its behaviour towards iodine and methyl violet, and by its insolubility in acid solutions of pepsin.

Since, then, amyloid is nothing but a peculiarly modified albuminous body, the substance from which it has arisen, cannot be far to seek. Yet, for the elucidation of the entire

* Cornil, 'A. d. phys.,' 1875, p. 671; Heschl, 'Wien. med. Wochenschr.,' 1875, No. 32, 1876, No. 2; Jürgens, 'Virch. A.,' lxv, p. 189.

† Kekulé, 'Heidelberg Jahrb.,' 1858.

‡ Kühne und Rudneff, 'Virch. A.,' xxxiii, p. 66.

process, little is gained by the mere knowledge that such a connection exists—especially as we are unaware even in what organs and where the transformation of ordinary albumen into the amyloid form takes place. In seeking to obtain information on this point from the localities containing the material, it appears desirable to distinguish between two forms in which the amyloid degeneration is manifested. In the first place, the substance is not very rarely met with in *isolated* spots, either as microscopic masses and bodies, or in the shape of considerable tumour-like nodules; it has thus been found in the conjunctiva,* in fibrous tumours of the larynx,† in cicatricial tissue,‡ in thrombotic deposits on the cardiac valves, and in the remains of old inflammatory infiltrations.§ But this local appearance of amyloid is less interesting, and certainly much less important pathologically than the same degeneration, *when it progressively involves a more or less large number of organs.* It was on this form moreover that the original description of Merkel and Virchow was based; and it is of it all pathologists think when they speak simply of amyloid degeneration. In it, the amyloid substance is most frequently found in the walls of the *vessels,* above all of the small arteries, but also of the capillaries, less commonly of the veins; in arteries and veins it is chiefly the muscularis that degenerates. The small vessels of almost all the organs of the body may be involved when the disease is extreme; yet this is very rarely observed, and the degeneration is ordinarily limited to the abdominal viscera, attacking by predilection the *spleen;* then the *liver,* and *kidneys;* and lastly the *intestine, lymphatic glands, suprarenals, omentum, mesentery,* &c. In some of these organs, however, the degeneration is not confined to the vessels; and it was long universally supposed, and is still regarded as certain by many writers,|| that certain other ele-

* Leber, 'A. f. Ophthalmol.,' xix, 1, p. 163, xxv, 1, p. 1; Stroehmberg, 'Ein Beitrag. z. Casuistik d. amyloid. Degeneration a. d. Augenlidern,' I.-D. Dorpat, 1877; Zwingmann, 'D. Amyloidtumoren d. Conjunctiva,' I.-D. Dorpat, 1879.

† Burow, 'Langenb. A.,' xviii, p. 2.

‡ Ziegler, 'Virch. A.,' lxv, p. 273.

§ Billroth, 'Beiträge z. patholog. Histologie,' Berlin, 1858.

|| Virchow, l. c.; Frerichs, 'Klinik. d. Leberkrankh.,' 2 Aufl., p. 165;

ments are capable of undergoing the amyloid change; these are the spleen-pulp; the hepatic cells, especially those of the middle zone; in the intestine, the fibres of Brücke's muscle, as well as those of the muscularis proper; and lastly the muscle-fibres of the heart and uterus. By others* this view has been strenuously opposed; and the most recent investigators have arrived at the conviction that amyloid degeneration is far from attacking the different elements indiscriminately, but *is an affection strictly limited to the connective tissues.* According to them, the process commences in the wall and sheath-like investment of the capillaries; or in the ground substance of the fibrous tissue; or in the transparent borders of dense connective substance, whereby the stroma is marked off from the contained specific parenchymatous elements: and it is not the muscle-fibres themselves, but the so-called perimysium internum and the cement-substance between them that undergo amyloid degeneration; similarly, in the liver not the cells but the stroma; in the spleen and lymphatic glands, not the pulp and lymph-cells, but the supporting trabeculæ. In fact the methyl-reaction allows of a very sharp localisation of the amyloid, and in many cases leaves no doubt that the parenchyma-cells proper are not implicated in the process. Even when no trace of the latter can be detected amongst the amyloid masses, the assumption that they have atrophied and finally perished under the pressure of the highly expansile amyloid substance is certainly no less probable than the hypothesis that they have themselves succumbed to the amyloid degeneration.

In all these localities, however different their nature, there is clearly no dearth of albuminoid substances, by whose transformation the amyloid might have originated. Yet we cannot *a priori* ignore the possibility that the material may not have originated in the locality where it is found, but have been deposited there, just as are the earthy salts in the pro-

Rindfleisch, 'Pathol. Gewebelehre,' 5 Aufl., p. 32; Böttcher, 'Virch. A.,' lxxii, p. 506; Kyber, 'Studien über d. amyloide Degeneration,' Dorpat, 1871; 'Virch. A.,' lxxxi, pp. 1, 278, 420.

* E. Wagner, 'A. d. Heilk.,' ii, p. 481; Neumann, ibid., ix, p. 35; Heschl, 'Wien. akad. Stzgsb.,' lxxiv, Abth. 3, Octob.-Heft; Cornil, 'Arch. d., physiol. norm. et pathol.,' 1875, p. 679; Tiessen, 'A. d. Heilk.,' xviii, p. 545; Eberth, 'Virch. A.,' lxxx, p. 138.

cess of calcification. In discussing from this point of view the conditions under which amyloid appears, it is above all necessary to notice that the disease, in its second form, has a markedly *progressive* character, so that, when of long standing, it is never confined to a single organ. True, it attacks in the first instance a definite locality—in the great majority of instances the spleen, where, in quite recent cases, the amyloid substance is often alone to be met with. But after a short time the disease invariably involves other organs, the kidneys, liver, intestine, or some other of those above mentioned. But its *etiology* still more evidently points to the dependence of the amyloid degeneration on *general* disturbances. It is an almost universally applicable rule that the individuals attacked by it are sufferers from some other severe disease of a chronic character.* Amyloid degeneration most frequently follows on *chronic tuberculosis,* especially of the lungs; the next largest contingent is supplied by *constitutional syphilis;* and then come *chronic suppurations, chiefly of the bones and joints,* but also of the *soft parts.* Compared with these three categories, all others fall into the background. Only occasionally does the lardaceous change supervene on *leukæmia,* on obstinate *intermittens,* further on *chronic dysentery,* and *gout.* In cancerous and sarcomatous cachexia it is extremely rare. The exceptional position occupied by these latter diseases is probably to be referred simply to the fact that amyloid degeneration is an exquisitely chronic affection, requiring even in the most favorable circumstances about three months† for its development, so that in cases of malignant tumour no time is allowed for its production. This view is supported by the frequent association of an early stage of the degeneration with comparatively benign and slowly growing carcinomata, *e. g.* colloid cancer. Lastly, I must confess that I, in common with other pathologists, have met with cases of very widely disseminated amyloid change, in which I absolutely failed to establish the presence of any other general disease.

What may be inferred from the foregoing as to the nature

* Cf. Hoffmann, 'Aetiologie u. Ausbreitung der Amyloidentartung,' I.-D. Berlin, 1868.

† Cohnheim, 'Virch. A.,' liv, p. 271.

of the process? A number of writers, Virchow, Rindfleisch, Ziegler, and others, decidedly incline to the opinion that *the amyloid substance is supplied to the affected localities in the transudation*, and, as it were, *infiltrates* them. Rindfleisch,* believes it most probable that an albuminous body contained in the nutrient fluid is arrested on its way through the tissue and there deposited in solid form. But whence, it may fairly be asked, is the amyloid albuminous body derived, and where is it produced? It can hardly be produced in the blood, for to say nothing of the disinclination one naturally feels to localising such a profound chemical process in this fluid, *no trace of amyloid has ever been found there*, even in the most intense and widely disseminated amyloid degeneration. It would be more easy to conceive of its production in some of the organs, and its removal thence to the blood; an amount equal to that entering the circulation being deposited elsewhere. The regularity with which the disease originates in the spleen might be held to favour this idea. Yet if stability be a characteristic of any substance, it is certainly so of amyloid, and anyone who has examined a sago or waxy spleen will be averse to the notion that the amyloid is here in the act of passing over into the blood, or is even destined to do so. Nor, so far as I can judge, does the localisation of the material make in favour of a deposition in, or infiltration of, the tissues from the blood. For instead of the equal distribution of the degeneration, on which so much stress has been laid, we find not only that various organs are involved on different occasions, but that in the spleen the degeneration takes place in one case in the follicles, in another in the capillaries of the pulp; in the kidneys the same variation occurs, the affection of the glomeruli sometimes preceding that of the vasa recta of the pyramids and sometimes following it. Moreover, even when we confine ourselves to a single tissue, we find no such regularity in its invasion by the disease. Anyone who has seen a large number of amyloid kidneys knows how often it happens in moderate cases that some of the glomeruli, or at least tufts, remain completely unaffected, while in the liver the greatest irregularity in the amyloid degeneration of its different portions is even the rule. In these

* Rindfleisch, l. c.

circumstances, so far as I see, the infiltration-hypothesis can be maintained only on one of two suppositions—either that a corpuscular, and not a fluid substance, is deposited in the affected tissues from the transudation, or that the places in which the deposition takes place are in some special way predisposed thereto, the predisposition depending on unknown, but certainly *acquired*, properties. But if this be admitted, it appears to me more simple on the whole to regard the entire process as *a local degeneration conditioned by general causes*—a degeneration in which consequently the amyloid substance is directly derived *from the pre-existing albumen of the tissue.* The appearances found in extreme cases of amyloid disease are no less compatible with this assumption than with the theory of infiltration; in certain slighter degrees of the affection they may, I think, be much better explained—or rather can only be explained—on our hypothesis. I have in mind those cases with which every experienced pathologist is familiar, where, with marked amyloid of the spleen, some of the glomeruli are a little more brilliant than others and stain somewhat more deeply with iodine, though the tint assumed by them is not reddish brown, but at most a deep orange; and where also methyl-violet gives an indefinite shade of colour between blue and red. Here we have, I believe, an intermediate stage in the transformation of ordinary albumen into amyloid. For to regard the transformation as sudden, or completed at a stroke, would most certainly be erroneous; it consists rather in a gradually progressive and evidently chronic process, the last stage in which is the amyloid material with its typical reactions. Now, on reflecting how much this very chronicity tends to obscure our insight into the intimate relations of the process, you will not be much surprised at our knowing no more of the conditions under which the albumen of the organs becomes indigestible than of the factors on which cloudy swelling or mucous metamorphosis depends.

Any attempt to determine how amyloid degeneration influences the function of the tissue affected is attended by the greatest difficulty, because in the first place the disease does not (*e. g.* in the liver) involve the whole of an organ, but chiefly because the affection is almost invariably met with in

persons who are suffering from some other severe general disease. When, and where, the cells are caused to disappear completely, or almost completely, by the waxy degeneration, any performance of function by them is of course out of the question. But whether their function is impaired in the earliest stage of the degeneration is uncertain, nor have we any knowledge of a reconversion of the amyloid substance; though the occurrence of such is certainly quite conceivable *a priori*. The question of deranged function assumes its most important aspect in connection with amyloid degeneration of the vessels; and I have had already (vol. i, p. 246) to acknowledge how little we know of the circulatory disturbances called forth by it. For that lardaceous disease of the vessels is not without its effect on the circulation is to be inferred, as I then stated, from the fatty changes usually undergone by the cells supplied by the amyloid vessels, as well as from the *albuminuria* and the watery *diarrhœa* which regularly accompany the degeneration of the renal glomeruli and the vessels of the intestinal mucous membrane. The alteration sustained by the urine as the result of amyloid degeneration of the renal glomeruli—which will be minutely described when we come to deal with the pathology of the kidney—has often been the means of showing that the amyloid substance may remain for many years unchanged. The fact that the degeneration is stationary in certain cases does not of course militate against the possibility of healing—*i. e.* disappearance of the lardaceous material—in slighter degrees of the affection.

We shall not discuss the so-called *amyloid bodies of the prostate* nor the *corpora amylacea of the nervous system* and perhaps *lungs,* for I have nothing to add to what you already know on this subject from pathological anatomy and histology;* and as their chemical nature has not yet been suffi-

* Purkinje, 'Bericht über die Prager Naturforscherversammlung,' 1837; Virchow, 'Cellularpathologie,' pp. 323, 435; his 'A.,' vi, pp. 135, 416, and elsewhere; 'Würzburg Verh.,' ii, p. 51; Friedreich, 'Virch. A.,' ix, p. 613, x, pp. 201, 507, xxx, p. 385; Leber, 'A. f. Ophthalm.,' xix, pp. 163, 191; Paulitzky, 'Virch. A.,' xvi, p. 147; Langhans, ibid., xxxviii, p. 536; Zahn, ibid., lxxii, p. 119.

ciently established, I deem it advisable to refrain meanwhile from hypotheses as to the mode of their formation.

The *abnormal colourations* so very commonly met with in all sorts of pathological conditions may also be briefly dismissed.* For when treating of hæmorrhage we thoroughly discussed the most usual, and hence most important, mode of pigment-formation (vol. i, p. 409). I shall therefore merely remind you here that crystalline or granular *hæmatoidin* originates in liberated blood-colouring matter, while cells which have taken up red blood-corpuscles convert these into granules and masses of *pigment;* and that we also admitted it possible for red corpuscles to become by shrivelling directly converted into granular pigment. In some one of these ways, or by a combination of them, is formed not only the pigment of all *apoplectic cicatrices,* but also that of the *corpus luteum, brown induration of the lung, hæmorrhagic pachymeningitis, nutmeg-liver, cicatrised ulcers of the skin,* &c. The pigmentation in these cases is always attributable to blood-corpuscles which have for some cause or other forsaken the blood-vessels, *i. e. extravasated.* But when we come to deal with the pigment present *in the interior of the vessels,* the question is much more complicated. Pigment is occasionally found in this situation in brown induration of the lung, and is regularly present here in so-called *melanæmia,*† following severe intermittent fever. That it is derived from hæmoglobin is proved by the contained iron,‡ and would in any case hardly be questioned; the only disputed point is whether it originates within or outside the vessels. Orth§ believes that the pigment in brown induration of the lungs is formed in capillaries which have been cut off from the circulation, and in which therefore the blood has become stagnant. On the subject of melanæmia

* On production of pigment from blood-colouring matter see vol. i, pp. 407, 409, footnotes; Wagner, 'Handb.,' p. 426; Perls, 'Lehrb,' i, p. 213, treats very thoroughly of the formation of the various pigments.

† H. Meckel, 'Zeitschr. f. Psych.,' iv, Heft 2; Virchow, his 'Archiv.,' ii, p. 587; 'Cellularpath.,' p. 263; Heschl, 'Oesterr. Zeitschr. f. pract. Heilk.,' 1862, Nos. 40—43; Frerichs, 'Klinik d. Leberkrankheiten,' i, p. 325.

‡ Perls, 'Virch. A.,' xxxix, p. 42.

§ Orth, ibid., lviii, p. 126.

there are two opposite views. According to one, upheld by Virchow and Frerichs, the pigment originates in the spleen and liver, and passes from these organs into the blood. According to the other, which has recently been defended by Arnstein,* a number of red corpuscles perish in the interior of the vessels during the pyrexial attack, thus giving rise to granular pigment. Partly by the agency of colourless blood-corpuscles and in part directly, this pigment is then deposited in those organs which in general form resting-places for corpuscular substances derived from the blood, namely the *spleen, liver,* and *bone-marrow.* Certain it is that in the bodies of persons who have passed through pernicious and severe intermittent attacks the pigment is found after years have elapsed in the last-named localities, being contained chiefly in comparatively large cells lying in the neighbourhood of the vessels. At the same time it is no less certain that granules and flakes of pigment may occasionally be detected in the blood a very long time subsequently to the last pyrexial attack.†

The presence of ochre- and rust-coloured pigment, originating in blood-colouring matter, in all varieties of *tumours* is naturally to be expected, when we remember the extreme frequency of hæmorrhage in them. There, are, however, certain tumours which are specially distinguished by the large amount of pigment contained in their cells. These are the *melanomata, melanotic sarcomata,* and *melanotic carcinomata,* and here it is by no means certain that the smoky grey to brownish black pigment granules have originated in a metamorphosis of blood-colouring matter. These pigments are not rendered blue by ferro-cyanide of potassium and hydrochloric acid, and iron has often been unsuccessfully sought for in the ashes of melanotic tumours.‡ But we know nothing of any other mode in which pigment may originate, and this deficiency in our knowledge is not covered by the fact that melanosis in man almost always starts in a region the cells of which normally contain pigment, as *e. g.* the choroid and pia mater cerebralis, and, for the rest, shows a

* Arnstein, 'Virch. A.,' lxi, p. 494, lxxi, p. 256.

† Mosler, ibid., lxix, p. 369.

‡ Perls, l. c.

special predisposition for animal *varieties poor in pigment*, *e. g.* white horses.

There are, in any case, pathological pigmentations not directly related to the colouring-matter of the blood. We have, in the first place, the *icteric colouration*, which is due, you are aware, to the passage of free bile-pigment from the blood into the transudations. The intensity of the tissue-staining depends of course on the quantity of colouring-matter entering the transudation; in extreme cases the hue may be green or even a black-green—*icterus viridis* and *melas*. In such cases the pigment does not remain completely dissolved, but is usually thrown down in the form of angular or rounded particles of a brown colour, which are then met with *e. g.* in the renal epithelium and hepatic cells. Similarly the *deep orange hue of atrophic adipose tissue* depends on the persistence in the fat-cells of the pigment peculiar to fat, after most of the fat itself has disappeared in consequence of the atrophy.* Moreover, the brown pigment of atrophic muscles, especially characteristic of brown atrophy of the heart, must be attributed to the greater resisting power of muscle-pigment, as compared with contractile substance, toward conditions productive of atrophy. It is somewhat improbable, lastly, that the pigment filling the cells of the rete Malpighii in "bronze-skin" or Addison's disease has originated in a direct metamorphosis of blood-colouring matter. At any rate it contains no iron, and, in view of the almost constant occurrence of caseation of the suprarenals in this disease, one can hardly avoid supposing that the pigmentations of the skin and mucous membrane are somehow related to those peculiar colouring-matters, the material for the formation of which would appear, according to the researches of Arnold and others, to be contained in the suprarenal capsules.†

We are still without any explanation of the affection called by Virchow‡ *ochronosis*, *i. e.* a deep brown to grey black dis-

* Kühne, 'Physiol. Chemie,' p. 370.

† Addison, 'On the Constitution and Local Effects of Disease of the Suprarenal Capsules,' 1855; Averbeck, 'Die Addison'sche Krankheit.,' 1869; J. Arnold, 'Virch. A.,' xxxv, p. 102; Vulpian, 'Compt. rend.,' 1856, xliii, No. 13; Kühne, 'Physiol. Chemie,' p. 415; for the literature of Addison's disease see Merkel, in Ziemss. 'Handb.,' viii, 2, p. 283.

‡ Virchow, his 'A.,' xxxvii, p. 212.

colouration of the cartilages and intervertebral discs, as well as of the intima of the arteries and synovial membranes, which was accidentally discovered in the body of an old man. In this case there was an evenly diffused saturation of the intercellular substance with the pigment.

CHAPTER VI.

REGENERATION AND HYPERTROPHY. INFECTIVE TUMOURS.

Laws and conditions of physiological growth.—Inherent cause —the productive capacity of the elements.—External cause —adequate supply of blood.—Unequal growth of the various tissues and organs.—Causes of this inequality.—The influence of waste on growth.

Enlargement as the result of diminished waste.—Hypertrophy of the osseous system from chronic phosphorismus. —Infarct of uterus.—Pathological regeneration.

Hypertrophy due to increased blood-supply.—Hypertrophy in vascular neuroses.—Pathological work-hypertrophy of muscular organs. Vicarious hypertrophy of glands.—Callus and clavus.—Hypertrophies depending on inflammation.—Ichthyosis, warts, and condylomata, chronic catarrh.—Atypical growth of epithelium.—Increase in bulk of connective tissue, lymphatic glands, and spleen the result of inflammation.

Fever-spleen.—Endemic goitre.—Leukæmic hypertrophy.

Forms, and further history, of the hypertrophies.

Infective tumours of syphilis, glanders, tuberculosis, lupus, lepra, "pearly disease."—Transmissibility of tuberculosis.—Incubation of inoculated tuberculosis.—Human tuberculosis and scrofula from the standpoint of infection. Anatomical accordance of the infective tumours.—Their near relationship to inflammation.—Probable identity of tuberculosis and "pearly disease."—Actinomycosis, lymphosarcomatosis.—Imperfect acquaintance with the histological development of the infective tumours.

The third group of nutritive disturbances embraces a number of processes which, though differing among them-

selves, agree in one point—the attainment of a greater size by the affected part than in the same interval should normally be the case. The *pathological regenerations, hypertrophies,* and *tumours* belong to this group. A moment's consideration will show that all these processes must depend on a disturbance of the normal equilibrium between *apposition* and *consumption* in favour of the former. I know of no other way in which an actual increase of tissue could be brought about than by the preponderance of tissue-formation over tissue-waste. Such a relationship, I need hardly say, is not under all circumstances an unwelcome one ; during the entire period of growth it is the typical and regular condition. Physiological growth is the natural type of the pathological new-formations, or, as they are termed, the *progressive disturbances of nutrition ;* and in attempting to gain an insight into the conditions on which the latter depend, our most obvious plan will be to take the laws of normal growth as starting-point.

The ultimate and essential ground of all growth is, as you know, the organisation of the particular species. It is to *inherited,* if I may so say, *historical* causes that we must ascribe the fact that the body and individual organs of each member of a species attain a certain size and shape, and that an approximately equal time is occupied in development by each species ; moreover it is owing to these from the first *inherent* influences that the growth of the single organs is so extremely unequal. As is well known, the nervous system grows most rapidly at first, while later on the growth of the muscles and bones as well as of the epithelial organs overtakes it. The thymus has reached its maximum in man before the end of the first year of life, while the extremities go on increasing in length till after the twentieth year; and in the genitals vigorous growth does not commence till puberty. All these, and the other differences in growth, with which you have become acquainted from normal anatomy are no less the result of the organisation transmitted by inheritance than are the equally striking diversities in the atrophic or retrogressive processes of physiological life, to which reference was made on a former occasion (vol. ii, p. 608).

The inherited, and therefore radically inherent, quality is, it is evident, the *capacity for growth.* The elements of the

embryonic germinal tissue, the leaf-like layers of the blastoderm, and later on the organs of the embryo, fœtus, and child have the power of assimilating suitable material when it is presented to them, of thus increasing in size, and thereupon of producing new elements from themselves ; and this power they possess to a degree very much in excess of what would be required for their maintenance intact, or, in other words, for the repair of immediate waste. But it is no less evident that for growth to take place, suitable material must be placed at the disposal of the elements concerned. During intra-uterine existence the necessary material is supplied by the maternal organism, after birth by the food; and none of you will expect a poorly fed child to increase in weight like a well-nourished one. For the individual organs, the blood and transudation have the same importance as has the food for the entire organism. The extremity of a child may have its growth retarded, it may even become smaller and dwarfed, if for any cause its blood-supply be much interfered with ; and it would undergo necrosis, just as in the adult, on being completely robbed of its arterial supply. The presence of a sufficient quantity of appropriate material is in a sense an indispensable *external* condition of normal growth. If this condition be complied with, and no direct disturbing or inimical factors, such as abnormal temperature, be present, development and growth will take place in a healthy individual within limits corresponding to his age. No other positive condition is needed, and in particular, you will notice, no *innervation.* That intra-uterine growth may take place in the most regular and perfect manner in the absence of all innervation is shown beyond question by the full, thoroughly normal, and even powerful development of all the internal and external organs in monstrosities without brain or cord, the *anencephalia* and *amyelia.* Moreover, repeated pathological observations on hemiplegic extremities in children clearly prove in how great a degree normal and regular growth is independent of innervation.

If then the growth of a part is effected through the assimilation by its elements of a larger quantity of material than is needed for the repair of waste, and the appropriation of this excess to the production of new elements, it follows

that a part must *cease growing when the productive power of its elements is exhausted, or when the supply of material is no longer in excess of the consumption.* In fact, it is a conclusion readily suggesting itself that the cessation of growth in man after the twenty-second year is simply due to his body having become so large that all the material he can command is just sufficient to maintain the organs intact. Yet however apposite this view may be in its broad outlines, it is no explanation of the facts of the case, as is apparent from the striking inequality of the various organs as regards amount of growth and the time occupied in growing. The question why an adult man stops growing cannot, in my opinion, be answered in general terms, but must be specially discussed for each individual organ or tissue. For all tissues have not the same inherent capacity for production. On the contrary, the productive energy declines much earlier in some than in others, and in a few instances becomes extinct at a time when it is elsewhere extremely vigorous. Proofs of this are not far to seek. The atrophy of the thymus in the second year of life, *i. e.* at a period when growth generally is most energetic, takes place simply because the productive power of the thymus-cells is extinguished. The elongation of the bones is, as you know, a function of the epiphysial cartilages; when the formative power of these cartilages is exhausted and the cartilage itself used up, a stop is put to growth in an axial direction. The central nervous system also appears to completely lose its productive power on the termination of growth; no vestige of regeneration after morbid losses of central nerve-substance has ever been observed in the higher animals.* In these cases, then, cessation of growth is due simply *to the extinction of the productive capacity of the tissue-elements;* and it is therefore quite immaterial whether the blood-supply be plentiful or scanty. The most intense congestion of the vessels of the anterior mediastinum could not postpone the atrophy of the thymus beyond the second year of life, nor could the most marked hyperæmia cause elongation of the bones of the extremities in an adult. But this is very far from true of the muscles and glands, still less of the superficial epithelium. For the capacity for apposing new material

* Schiefferdecker, 'Virch. A.,' lxvii, p. 542; also contains the literature.

does not in these tissues cease with the termination of growth. Every muscular contraction, every secretion of a gland, is accompanied by a waste of muscle and gland-substance, and actually occurs at the expense of these substances; and the decrease in bulk which would otherwise result is prevented simply by the constant fresh apposition of contractile material and of gland-cells. The same may be said of the spleen and lymphatic glands; while as regards the superficial epithelium, in no tissue has a continuous new formation of cells to replace the superannuated ones, lasting during the entire life, been so conclusively proved. If then it cannot be doubted that the elements of the last-named tissues are permanently endowed with a capacity for production, why, we naturally ask, do not the muscles grow after the twenty-second year; why do not the glands become larger, and the layers of epithelium thicker?

But is it really true that the muscles and glands of an adult never increase under normal circumstances, and that the epithelial covering never grows thicker? Most of you will, I think, have learned from your our bodies that the muscles may be increased in volume; and on calling to mind the arm-muscles of our smiths and coopers any doubt on this point will seem strange. Who does not know, besides, how greatly the epidermis of the hands is thickened in labourers and artisans? The cause of this excessive growth is evident enough: it is the result of an abnormally abundant assimilation, which is itself made possible by a lasting or an oft-repeated abnormal increase of the blood-supply to the parts in question. In the muscles it is the congestion taking place during work that brings about the increased blood-supply; in the hands it is the ever-recurring fluxions called forth by the repeated mechanical irritation to which the parts are exposed. But here we have also the explanation of why it is that organs endowed with a capacity for production do not usually produce beyond the limits set by internal causes. To do so, they would require before all things an *increased supply of blood continued for a considerable time.* Now this, as you know, is impossible as a lasting condition unless the total blood-quantum be increased. But the amount of blood in the body does not, you are aware, vary with the nourish-

ment taken; it is an approximately constant quantity, and depends upon the relations subsisting between blood-consumption and the activity of the hæmapoietic organs. Now in the adult, the work of the latter consists merely in replacing that portion of the blood which has been applied to the maintenance of the organs intact, these organs displaying their ordinary functional activity. That the blood-forming organs can do more than this is beyond question; but before doing it, they require a special stimulus, which is not afforded by a mere increased absorption of nutriment, but solely *by an extraordinary demand for blood on the part of the various organs of the body.* It is of course impossible for the hæmapoietic apparatus to produce more blood than usual, except at the same time the supply of albumen, iron, salts, water, &c., be augmented; but it would be a great mistake to suppose that more blood is produced *because* more material is supplied to the body. When any one takes more animal food than usual without altering his mode of life, you know what happens: he simply excretes more nitrogen in his urine, or at most accumulates fat. In the case supposed by us the converse relation obtains. The individual who goes through much muscular exertion requires a larger quantity of blood; this can only be secured by increased function of the blood-forming organs; and to this end the individual instinctively takes a larger amount of albumen, iron, &c., in his dietary, and partakes of more animal food than before; although, as is well known, the work of the muscles is not itself performed at the expense of nitrogenous substances. When, however, the total quantity of blood in the body is increased in this way, to such an extent that the working muscles can permanently receive an abnormally large amount of blood without impoverishing the other organs, the muscles of the adult also increase; not, it is true, in length—this the unalterable length of the bones prevents—but in *thickness,* in cross-section.

The mechanism which effects the augmented supply to, and assimilation in, muscle under these circumstances is known to be nervous; *nervous influences* cause dilatation of the muscular arteries during work, as well as increased waste and repair of material. While, then, as already stated, the enlargement of muscle during the growing period proper is to

a great extent independent of innervation, a muscular increase never occurs after growth is completed without the definite co-operation of the nervous system—a co-operation which, I need hardly say, may also exert a modifying influence during the period of growth. Precisely similar conditions hold good for a portion at least of the smooth musculature—that of the intestines, for example—though, as you are aware, it has not yet been certainly demonstrated that the unstriped muscle of other parts is dependent for its activity on nervous influence. On the other hand, a nervous relation of this kind has been clearly made out for a number of glandular organs, and it is not possible for the salivary glands, pancreas, or testicles to grow after the body has reached its full stature except *as the result of increased work through nervous stimuli.* In the case of glands, however, which like the kidneys and perhaps the liver are not so directly dependent on the nervous system, it cannot of course be nervous influence that brings about any chance enlargement after bodily growth is complete. To cause their enlargement it is necessary that the energetic and prolonged action of certain factors, having the power of directly stimulating the gland-cells and dilating the arteries, should come into play. If, for example, according to an hypothesis formerly dwelt on (vol. i, pp. 115, 133), the calibre of the small renal arteries and the work done by the renal epithelium are determined by the amount of material destined for excretion with the urine from the circulating blood, the kidneys of an adult will not hypertrophy except these effete matters have for a long period been present in considerable quantity in the blood. An analogous observation may be made with regard to those unstriped muscles which are stated to be stimulated by some other than nervous agencies.

The reason I attach so much importance to the dependence of these organs and tissues for their activity on stimulation—embracing as they do all the working organs proper of the body—will at once be apparent on recalling to mind that their elements *do not,* so far as we know, *assimilate except when stimulated.* A muscle bathed by an abundant blood-stream will not therefore contract, any more than a gland will secrete for the same reason. Hence it is not at all surprising that a muscle or a kidney does not grow, despite intense and long-

continued inflammatory hyperæmia. But how is it with regard to those tissues which have no actual work to perform, and to whose elements we do not usually ascribe a "function" in the strict sense of the term? The function of the superficial epithelium, and of the connective tissues, bone and cartilage included, essentially consists, if I may so say, *in their existence*; we know nothing, at any rate, of any alteration of their physical or chemical constitution depending on stimulation. All assimilation and new formation, when occurring in these tissues, must consequently be due to those conditions on which their growth proper depends, *i. e.* inherent productive capacity and amount of blood-supply. Now, I need hardly show that the capacity for new formation in epithelia, as well as in connective tissues—including under the latter term blood- and lymph-vessels, lymphatic glands, together with bone and laxer fibrous tissue—persists till very late in life, and thus there is but a single factor by which the degree of apposition in these tissues is regulated, namely, *the amount of material, i. e. of blood, supplied them.* Hence not only do the walls of the vessels become thicker, when the blood flowing through them is permanently increased, and the long bones of persons going through much muscular exertion grow more bulky, but every chronic inflammatory hyperæmia invariably leads, as you well know, to a new formation of vessels and fibrous connective tissue, or of bone, if the hyperæmia involves the periosteum. As to the stratified epithelia, I shall soon have to acquaint you with similar facts. There is therefore not a particle of doubt that the usual non-occurrence of any increase in bulk in the tissues last mentioned after the twenty-second year of life is merely due to the absence of sufficient material. For a bone or the epidermis to become thicker, the vessels of the periosteum or the cutis must be supplied for a long period with an abnormally large amount of blood; but the blood-quantum of an adult is not sufficiently copious to admit of this, if the remaining organs are to receive their regular supply.

One point there is, indeed, which must not be overlooked in this discussion, namely, *the amount of tissue-consumption.* For it is evident that the most extensive and energetic apposition cannot lead to enlargement of an organ, if the con-

sumption be increased to keep pace with it. Were I here to discuss the conditions of normal bodily waste, and the forms in which the various organs and tissues yield up their material, I should only reiterate what you already know, and what moreover has repeatedly been referred to in these lectures. The growing period proper is definitely characterised by the excess of apposition over the consumption occasioned by the activity of the organism or the accomplishment of its ends. The number of newly formed cells in the rete Malpighii is greater than the number of cornified cells cast off; more bone is apposed than is resorbed; and more contractile substance added than is used up during, and as the result of, muscular activity. In contrast to this stands the condition of the adult, in whom the equable maintenance of the size of the body, as well as of the individual organs, depends on the establishment of an equilibrium between apposition and consumption. Yet the means the organism adopts to secure this equilibrium cannot be stated in a few words or in general terms. Except for a few tissues, like bone and epidermis, we are unacquainted with the morphological processes whereby apposition and consumption take place; and even with regard to muscle—so often the subject of study—much remains to be cleared up before our knowledge of the metabolism of contraction can be said to be complete. In no case is it for a moment to be supposed that a mutual relation of dependence subsists between apposition and consumption, such as would lead throughout to the apposition of much new material whenever and because much was used up, and conversely. A nail left unpared does not therefore at once cease growing; and when for any reason the cells of the epidermis fail to cornify and consequently to be shed, the formation of cells in the rete Malpighii is no less abundant than before. The arrangements of the organism are not so simple; apposition has its own conditions, just as have consumption and loss; and it is precisely because of this mutual independence that consumption must be regarded as one of the factors by which the size of the individual organs is determined.

Let us now sum up these, it must be confessed, very fragmentary observations on the conditions of physiological

growth. We have seen that the first, and certainly the most important, point is *the productive capacity of the cellular elements,* determined by the organisation of the species or the individual. It is on this internal cause that the acquirement of the definite human form during the human growing period depends, and on the same inherited cause depends also the fact that different individuals attain such different sizes on the completion of growth. Without this inherent productive capacity the most copious supplies of nutriment must fail to bring about growth; and when the capacity is extinguished in the elements of a tissue, no power on earth can cause its further development. But provided the productive capacity be present in undiminished energy, the growth and size of the particular organ, or tissue, depend on the quantity of material assimilated; hence on the *amount of blood-supply,* and, in the second place, *on the amount of consumption.* Three factors only are known to exert an influence on the growth of the organs and tissues—*inherent predisposition, blood-supply, consumption;* and we may, or rather must, logically conclude that in every case of growth in excess of the physiological standard, *i. e.* in all progressive derangements of nutrition, the behaviour of one or more of the above-named factors has been abnormal or defective. Such being the state of affairs, it is at least worth while to attempt a discussion of the progressive nutritive disturbances from the stand-point of the conditions of growth.

We shall first turn our attention to the last of these conditions, *i. e.* consumption, since it is the simplest and most easily comprehended. We have to examine *whether a progressive derangement of nutrition dependent on diminished waste at all exists, and if so, in what form this derangement is manifested.* The loss sustained in the normal course of things by the organs results, as you are aware, from expenditure in two fundamentally different directions—material being given up, in the first place, to the lymph and blood, and, in the second, to special preformed canals and cavities, or directly outwards. The delivery of material to the lymph and blood is the sole mode of consumption in muscle and all connective tissues, including bone, while in all glands and

glandular epithelia, as well as in the stratified epithelia, more especially the epidermis, the yield to blood and lymph, though not altogether absent, is completely overshadowed by the loss of material directly outwards, or into canals and cavities. The process of fattening teaches that a tissue may, and very commonly does, increase in bulk as the result of diminished loss to the lymph and blood. For when, under circumstances favorable to fattening, *i. e.* when oxidation is defective, the adipose tissue increases in amount, this merely indicates an abnormal reduction in the quantity of fat passing over into the lymph and blood. We have, however, in this instance to deal with an accumulation of a definite chemical substance, the fat, in the tissue-cells rather than with an actual increase of tissue; and you will therefore ask for more convincing examples before admitting the possibility of an actual hypertrophy as the result of diminished expenditure. As regards the connective tissues we are acquainted with no facts which *must necessarily* be interpreted in this sense, but Wegner has succeeded in experimentally producing an hypertrophy of bone, the essential and determining element in which is in all probability the limitation of osseous resorption. Rabbits, cats, hens, and other animals show a considerable *thickening of all their bones* after the administration of minimal doses of phosphorus for some months. Both the epiphysary and periosteal zones are affected; the spongy substance of the hollow bones, especially in the neighbourhood of the epiphyses, is often replaced by a really dense compact tissue, while the thickness of the diaphysis is considerably increased at the cost of the medullary cavity, which in hens may almost completely disappear. Wegner himself, it is true, explains these extremely interesting results as the products of an abnormally abundant new formation of bone excited by the phosphorus, yet Maas* has brought forward good grounds for believing that the chief effect of the phosphorus is interference with the *process of resorption*. That deprival of oxygen is really, as Maas considers, the efficient agent, I cannot look upon as proved, but the situation and anatomical arrangement of the abnormal osseous tissue in chronic phosphorismus make it

* Wegner, 'Virch. A.,' lv, p. 11; Maas, 'Tagbl. d. Leipz. Naturforscher-versammlung,' 1872, p. 171.

probable that those portions of the bone, which would in normal growth have disappeared, here remain intact. This view, at any rate, affords the simplest explanation of the facts that the hyperostosis attains much larger dimensions in growing, than in fully grown, animals, and that the diaphysis is thickened at the cost of the medulla, *i. e.* of that portion of the bone which plays such an important *rôle* in the resorption of osseous substance. If this interpretation be correct, we have here a genuine and unquestionable textural increase of bone—a hyperostosis in the proper sense of the term —which is essentially due to a diminution in the amount of material yielded up to the lymph and blood. Almost more striking were the results arrived at by Maas, and especially by Gies,* on administering minimal doses of arsenic to young rabbits, hens, and pigs with their food for a considerable period. For the increase of tissue was not here confined to the skeleton; the animals experimented upon grew altogether larger and stronger; their superficial fat increased, in short they prospered decidedly better than the control animals of the same birth which got no arsenic. These experimental results, which for the rest perfectly accord with the well-known facts regarding the Styrian arsenic eaters, are also to be explained, in the opinion of the authors just mentioned, on the supposition of a diminution of waste brought about by the arsenic. Yet I must not conceal from you that direct investigation into the influence of minute doses of arsenic on the metabolism do not, so far, tend to support this view.†

You will hardly expect a similar condition of things to prevail in the muscles. For a muscle which consumes little, *i. e.* does little work, not only fails to increase, but decreases in bulk, simply because, owing to the absence of nervous excitation thereto, it ceases to assimilate. Nevertheless, one of the most beautiful illustrations of a pathological enlargement following diminution of tissue-waste is afforded by a muscular organ—an organ which, it is true, is distinguished from all other muscles by the fact that it grows after the termination of the growing period proper, and attains considerable dimensions, *without doing any work whatever.* I

* Gies, 'A. f. exp. Path.,' viii, p. 175.

† S. Voit, in Hermann's 'Handb. d. Phys.,' vi, 1, p. 181.

refer to the *uterus*. With its hypertrophy during pregnancy we shall deal later on; here I wish to remind you that the uterus, after expulsion of the fœtus, undergoes a physiological atrophy, which is effected solely by an extraordinary yield of material to the lymph and blood, so far at least as the muscular substance and intermuscular connective tissue are concerned. It not uncommonly happens that involution is interrupted before the uterus has dwindled to the normal size of the unimpregnated organ. We find in consequence an organ considerably enlarged in all its dimensions, consisting chiefly of hypertrophic and abnormally abundant muscle-fibres, very plentiful intermuscular connective tissue, and strikingly thick-walled vessels—in short the condition only too familiar to gynæcologists, and usually termed *chronic metritis*, chronic *hyperplasia* of the uterus, or *chronic uterine infarct*. It is not to be denied that chronic inflammatory changes, especially in connection with the mucous membrane, may also commonly be present; but the essential feature—that which impresses upon the entire process its proper character—the enlargement, depends on nothing but a reduction of waste below the physiological standard. In other words, *the chronic uterine infarct is a true progressive derangement of nutrition dependent on diminished consumption.*

Turning now to the second variety of expenditure—that into preformed cavities or directly outwards—the question arises whether the *glands* can ever undergo a textural increase as the result of a diminution of their secretion. To this we may unhesitatingly answer "no." For you will carefully distinguish between the discharge, and the production, of secretion. That obstruction to the escape of a secretion will lead to an increase in the volume of the excretory duct, and by consequence of the gland itself, is of course obvious. When the ductus Wirsungianus is occluded and the pancreas continues secreting, all the secretion which is not resorbed must accumulate in the ducts and finally in the vesicles; and the same may be said of a sebaceous or mucous gland, the opening of which is obstructed. When the secretion is abundant and the resorption slight, the amount of accumulated secretion may, or rather must, become really considerable; and this involves a more or less considerable increase in the

volume of the gland. The entire group of so-called *retention* or *dilatation-tumours,* forming the majority of all cysts, originates in a process of this kind; but so little is the enlargement in these cases due to a genuine textural increase of the glandular parenchyma that a *passive atrophy* of the gland tissue is regularly associated with every retention of secretion, if at all considerable in amount. A true textural increase of glandular parenchyma, an hypertrophy of the gland, could only be brought about by a cessation of the consumption of gland-cells in producing secretion, and the continued formation of new cells; but this is no more possible here than is an analogous effect in the case of the muscles, since assimilation and new formation in glands is dependent on the same stimulus that excites the secretion.

A regular increase of thickness, an actual hypertrophy, does, however, occur *in the epidermis when the epithelium is not so extensively shed as it should be.* This is very natural in the case of epidermal structures, in which separation is effected only artificially, namely, *hairs* and *nails;* for a hair or nail which is not cut must of necessity become abnormally long, provided at least that the growth of the nail-matrix and hair-bulb continues. But in the skin itself, washing with soap and water contributes not a little to the removal of the most superficial epidermic scales; and there is no doubt that the thickness of the stratum corneum of the labourer's horny hand is in a measure due to the fact that the cornified lamellæ not only escape softening by water and alkalies, but are even mechanically compressed and caused to adhere together by the manual labour—a circumstance which, instead of facilitating, must decidedly impede the shedding. It has already been stated that an increased production of epidermis, due to frequent congestive hyperæmia of the cutis, has also a share in producing this effect, and to its influence I shall have again to recur.

Nor, lastly, is there any doubt that diminished consumption plays an important part in *pathological regeneration.* When the pathologist speaks of regeneration, he does not refer to the process of repair continually going on in the normal condition of most tissues, but to the restoration of tissues which have perished through some abnormal influence,

as in wounds, ulceration, necrosis, &c. That this regenerative capacity is much more considerable in the invertebrate and lowest vertebrate classes than in man and mammals is doubtless already known to you. In lizards and tritons respectively the tail or leg when lost or cut off is reproduced; while in man and mammalia compound organs or parts of organs are never restored, regeneration occurring only in the tissues, and by no means in all of them. The most frequent opportunities for observing repair are afforded by the stratified epithelium. Every ulcer or wound of the skin clothes itself during healing with a newly formed epidermis, which is in no respect distinguishable from the old one. As to the morphological events making up this epithelial regeneration, all writers may now be said to agree in believing that the regeneration proceeds only from those portions of the epithelium which are situated on the borders or in the base of the epithelial defect. The highly interesting details of this process, which have been followed and described by a great number of writers*—Wadsworth and Eberth, Hoffmann, Heiberg, and with especial accuracy by Klebs—may properly be passed over in this place, since they could hardly afford us any information with regard to the causes of the epithelial regeneration. We need only point out that the result is essentially the same whether a layer of epithelium remains beneath the defect or the whole thickness of the strata is destroyed. In the former case the new formation of epithelial cells proceeds from the lowest existing layer; in the latter it is in the first place the epithelium of the periphery that contributes by its cell offspring to fill up the gap. Now, the new formation of epithelial cells in the lowermost stratum is, as you know, a physiological process that provides for the replacement of the elements continually lost by shedding from the most superficial layers. This being so, we may suppose *a priori* that every epithelial defect can, or rather must, be made good simply by the physiological new forma-

* Arnold, 'Virch.A.,' xlvi, p. 168; Thiersch, in Pitha-Billroth's 'Handb.,' i, Abth. 2, p. 531; Cleland, 'Journ. of Anat. and Phys.,' 1868, ii, p. 361; Wadsworth and Eberth, 'Virch. A.,' li, p. 361; F. A. Hoffmann, ibid., p. 373; Heiberg, 'Oest. med. Jahrb.,' 1871, p. 7; Klebs, 'A. f. exp. Pathol., iii, p. 125.

tion of epithelium, provided only the epithelium at the affected spot ceases to be shed during the time occupied in repairing the defect. This, however, is not merely a possible condition, but the shedding *must* in the present case of necessity cease for a time, as you will at once perceive, on remembering that only the cornified cells are cast off, and that cornification occurs, according to the type of our organisation, only in the uppermost cell-layers. It is precisely as though the total consumption, which would otherwise occupy days or weeks, had here occurred suddenly in advance, and the legitimate regeneration been reserved till afterwards. There can, in fact, be no doubt that such a temporary limitation of the shedding, of the consumption of epithelial cells, is an accessory in repairing a defect in stratified epithelium. But that it is not the only means adopted by the organism for this purpose is most clearly taught by the great rapidity with which the restoration of lost epithelium usually takes place. A moderately deep gap in the epithelium covering the anterior surface of the cornea becomes filled up within twenty-four hours; while for the regeneration of a total defect of 3 mm. diameter, thirty-six to forty-eight hours are sufficient.* For a task of such dimensions the ordinary physiological regeneration of epithelium is certainly too feeble. The cell-proliferation decidedly exceeds the normal standard of every-day life, so that factors giving rise to an *increased* new formation of epithelium must certainly be present.

All that has been said of stratified epithelium applies equally to the simple variety; and is indeed applicable generally to all tissues in which consumption and restoration are normally uninterrupted, provided naturally that the parts from which the process of repair proceeds have not also perished. For when a hair is pulled out it cannot of course grow again if the hair-bulb is absent; the gland-cells of the salivary glands cannot be regenerated without the demilunes; nor can the epithelium of the uterus be restored after delivery except the uterine glands, or at least their blind extremities, be intact. But if a regenerative cell-proliferation is rendered possible by the preservation of the matricular structures, there is apparently no reason why physiological regeneration should

* Cohnheim, 'Virch. A.,' lxi, p. 289.

not occur in tissues which have sustained a morbid loss of substance. If the periosteum preserves and evidences its power of apposing new bone during the whole of life, why, I ask, should it abandon this its function when, in consequence of a fracture or other destructive influence, larger portions of bone have been lost, that would in the same interval be removed in the normal process of continuous resorption? A temporary limitation or cessation of resorption must here also clearly be sufficient for the compensation of a defect, the length of time occupied in repair being determined chiefly by the extent of the defect. The same applies to the remaining varieties of connective tissue, to striped and smooth muscles, to the glands, and to the peripheral nerves. But though this is perfectly true, the participation in pathological regeneration of other processes than those of physiological repair may be much more strikingly demonstrated in these latter tissues than in the stratified epithelia. Not only does the pathological here far exceed in rapidity the ordinary regeneration, which we are in a position to estimate more especially in the case of bone, but in these tissues we with great regularity happen on certain forms which in a normal condition are seldom or never present in them. I may remind you, by way of illustration, of the long *lanceolate processes*, observed by Eberth* and Senftleben† in the fixed corneal corpuscles, and termed by the latter *regeneration-spears;* further, of the *muscle-spindles,* in regeneration of muscle, which have been noticed and described by so many observers;‡ and lastly, of the *narrow pale bands,* which, after bruising or division of a nerve, make their appearance in the interior of the old sheath of Schwann, afterwards become enveloped with white substance, and indicate that nerve-regeneration has commenced.§ Since, as has been said, there

* Eberth, 'Untersuchungen aus d. pathol. Institut zu Zürich,' Heft 2, 1874, p. 1; 'Virch. A.,' lxvii, p. 523.

† Senftleben, 'Virchow A.,' lxxii, p. 542.

‡ Cf. Kraske, 'Experimentelle Untersuchungen über d. Regeneration d. quergestreiften Muskeln. Habilitationsschrift,' Halle, 1878, contains numerous references to literature.

§ Waller, 'Müll. A.,' 1852, p. 392; Schiff, 'Ztschr. f. wiss. Zool.,' vii; 'Lehrb. d. Phys. d. Menschen,' Jahr 1858, i, p. 111; Remak, 'Virch. A.,' xxiii, p. 441; Neumann, 'A. d. Heilk.,' ix, p. 193; 'A. f. mikr. Anat.,' xviii, p. 302; Ranvier, 'Compt. rend.,' lxxv and lxxvi, No. 8; 'Gaz. méd.,'

is hardly ever a trace of these appearances in the normal cornea, or muscles, or nerves of a healthy individual, it is evident that they are due to some process other than physiological repair. Add to this that *tissue-formation in excess of the required amount* is extremely common in pathological regeneration—a circumstance which would be quite unintelligible if the effect were due merely to physiological apposition with temporary limitation of waste. These points, it appears to me, are especially characteristic of pathological regeneration. For its remarkable feature is not the occurrence, in tissues and organs undergoing continual waste and repair, of regeneration after morbid losses, nor the restoration of the lost tissue in the same form, at least up to certain limits; the striking point is the great vigour and rapidity with which in these circumstances regeneration takes place.

This character is, however, not difficult to explain on recalling one factor of such moment in the growth of tissues, namely, *the supply of nutrient material.* In the adult, those organs also whose elements have by no means lost their reproductive capacity maintain as a rule their size unvaried, because, so we argue, the nutriment at their disposal is just sufficient to cover the continual waste. This relation must, however, immediately be altered, when in any locality a considerable amount of tissue is lost through some cause or other. For even if the flow of blood and transudation in the affected part were to continue unchanged, the smaller organ with its reduced number of cells would have at command the same amount of nutrient fluid and materials capable of assimilation as the uninjured organ formerly had; or, in other words, the remaining tissue-elements would then be in a position to absorb more material, and consequently to produce more out of themselves than formerly. This condition is most obvious in non-vascular parts, where the nutrient vessels may escape implication in the process which has given rise to the defect.

1873, No. 9; 'Leçons sur l'histolog. du syst. nerveux,' Paris, 1878, i, p. 276; Eichhorst, 'Virch. A.,' lix, p. 1, contains reference to literature; Korybutt-Daczkiewicz, 'Degeneration u. Regeneration markhaltiger Nervenfasern nach Traumen,' I.-D. Strasburg, 1878; Dobbert, 'Ueber Nervenquetschung.' I.-D. Königsberg, 1878; Gluck, 'Virch. A.,' lxxii, p. 624; Falkenheim, 'Z. Lehre von der Nervennath u. d. prima intentio nervorum,' I.-D. Konigsberg, 1881.

A nail or hair which is not cut goes on growing spontaneously, it is true, but the longer it becomes the slower is its growth, till it finally ceases growing, because the supply of nutriment to the vessels of the hair-bulb is no more than sufficient to maintain the hair at the length then reached by it. After cutting, however, the same quantity of nutrient fluid is distributed to the elements of the now much shortened hair, and there commences, as everyone knows, a renewed growth, which is vigorous in proportion to the extent to which the hair was shortened. Whether we take a hair or some other part of the epidermis can clearly make no difference whatever. More than this, the foregoing considerations are equally applicable to other epithelial membranes, as well as to bone, tendons, or other connective tissue—in short, to all tissues in which waste and repair take place. Though we have here proceeded on the assumption that the blood-stream, and with it the supply of nutrient material, remains approximately unchanged in pathological defects and regenerations, yet you know from former lectures that this assumption is far from being always true. For only too often the production of a defect is followed by a genuine and pronounced *inflammatory hyperæmia,* by means of which the blood-supply and transudation are more or less augmented beyond the normal. And such being the case, it is not surprising that the regenerative new formation should now considerably surpass the physiological process of repair in extent and rapidity. Any exhaustive discussion of this point may, however, safely be dispensed with in this place, since we have already sufficiently considered its details in dealing with the terminations of inflammation (vol. i, p. 350, *et seq.*). On that occasion I called attention to the fact that the inflammatory hyperæmia affords a thoroughly intelligible explanation of the redundancy of the regenerative new formation—which, as a matter of fact, is chiefly noticeable when regeneration becomes complicated by inflammation. On the other hand, I also pointed out that severe forms of inflammation, the hæmorrhagic and more especially the purulent, instead of furthering, decidedly hinder regeneration, so much so, indeed, that under their influence restoration may not occur in cases where, without this complication, it never fails to be accomplished. True, the re-

instanced the highly developed muscles of gymnasts and labourers. In fact, enlargement and thickening of muscles, dependent on voluntary and forced exertion, cannot well be termed pathological. This title had better be reserved for muscular hypertrophies which originate independently of volition, and above all for those which result from an increased demand for work as the result of some morbid condition. The best examples of this mode of origin are the hypertrophies of the heart which arise in consequence of valvular defects, of synechia of the pericardium, or of other abnormal resistances in the vascular system, or which depend on abnormal increase of the heart's work from nervous causes. But the *hollow organs which are furnished with a smooth musculature* may also become the seats of most extensive hypertrophy when abnormal obstacles oppose the expulsion of their contents. Owing to stricture of the urethra, the muscle of the urinary bladder may become several times thicker than natural; in stenosis of the pylorus the musculature of the pars pylorica may be greatly increased in bulk, as may that of the intestine above a constriction.

Turning from the muscles to the glands, we find, on the boundary between health and disease, the enlarged kidneys and livers of persons who are in the habit of eating and drinking to excess. We have, on the other hand, a most beautiful example of pathological hypertrophy in the *vicarious* or *compensatory* enlargement of one of a pair of organs after destruction of its fellow. When one testicle is lost, the entire nervous stimulus to the production of semen is concentrated on the remaining organ; this involves a considerable increase of the blood-supply to the latter, and its hypertrophy is the result. When a kidney is destroyed owing to malformation, unilateral hydronephrosis, a large infarct, an abscess, or the like, a greatly increased demand is made on the work of its fellow, which may lead in a comparatively short time to an hypertrophy of the kidney to almost double its original size. A precisely similar explanation applies to the often observed sequence of hypertrophy of the lymphatic glands on extirpation of the spleen. In all these cases we have to deal with the conditions which we formerly learned were causes of lasting, so-called, *collateral fluxion;* and we

may therefore formulate a simple rule for the entire category—that hypertrophy occurs in all organs whose vessels are long the subjects of collateral fluxion. The thickening and increased volume of the congested vessels is simply a special application of this general law.

Work-hypertrophy is the natural privilege of the working organs. These organs cannot, for reasons formerly adduced, be stimulated to excessive growth by any other means ; while the tissues, on the other hand, whose function is not, strictly speaking, the performance of work, cannot be subject to work-congestion, and cannot, therefore, hypertrophy from this cause. But hypertrophy as the result of another variety of hyperæmia is proportionately common in them. Under this head comes first the thickening of the epidermis of the hand of the labourer, which, as I already stated, is chiefly due to the frequently recurring hyperæmia from mechanical irritation. While you may hesitate to regard the horny hand of the workman as something pathological, you will unhesitatingly admit this term to be applicable to the *circumscribed* thickenings of the epidermis, which are but too well known under the names of *induration* and *callosity*, or, when occurring on the toes, of *corn, clavus*. With respect to the latter, a wild suggestion has, it is true, in all seriousness been made —that they are due, not to a hyperæmia of the papillary bodies, but to a compression of the vessels and consequent imperfect blood-supply.* But if the writer referred to had devoted a little consideration to the mode of origin of corns, instead of satisfying himself with an examination of the fully developed growths, he would doubtless have hesitated somewhat before basing a complete theory of growth on the structure of a corn. For pressure upon the vessels of the papillary bodies at the affected spot is certainly, as everyone knows, the principal cause of clavus, but only in so far as the mechanical compression invariably leads on its subsidence to marked congestive hyperæmia. And it is this hyperæmia of the papillary bodies, repeated whenever the pressure of the boot is removed, that alone causes the increased growth of the epidermis at the spot pressed upon. If the pressure were unrelieved, there would most certainly be no induration,

* Boll, 'Das Princip des Wachsthums,' Berlin, 1876, p. 70.

instanced the highly developed muscles of gymnasts and labourers. In fact, enlargement and thickening of muscles, dependent on voluntary and forced exertion, cannot well be termed pathological. This title had better be reserved for muscular hypertrophies which originate independently of volition, and above all for those which result from an increased demand for work as the result of some morbid condition. The best examples of this mode of origin are the hypertrophies of the heart which arise in consequence of valvular defects, of synechia of the pericardium, or of other abnormal resistances in the vascular system, or which depend on abnormal increase of the heart's work from nervous causes. But the *hollow organs which are furnished with a smooth musculature* may also become the seats of most extensive hypertrophy when abnormal obstacles oppose the expulsion of their contents. Owing to stricture of the urethra, the muscle of the urinary bladder may become several times thicker than natural; in stenosis of the pylorus the musculature of the pars pylorica may be greatly increased in bulk, as may that of the intestine above a constriction.

Turning from the muscles to the glands, we find, on the boundary between health and disease, the enlarged kidneys and livers of persons who are in the habit of eating and drinking to excess. We have, on the other hand, a most beautiful example of pathological hypertrophy in the *vicarious* or *compensatory* enlargement of one of a pair of organs after destruction of its fellow. When one testicle is lost, the entire nervous stimulus to the production of semen is concentrated on the remaining organ; this involves a considerable increase of the blood-supply to the latter, and its hypertrophy is the result. When a kidney is destroyed owing to malformation, unilateral hydronephrosis, a large infarct, an abscess, or the like, a greatly increased demand is made on the work of its fellow, which may lead in a comparatively short time to an hypertrophy of the kidney to almost double its original size. A precisely similar explanation applies to the often observed sequence of hypertrophy of the lymphatic glands on extirpation of the spleen. In all these cases we have to deal with the conditions which we formerly learned were causes of lasting, so-called, *collateral fluxion;* and we

may therefore formulate a simple rule for the entire category—that hypertrophy occurs in all organs whose vessels are long the subjects of collateral fluxion. The thickening and increased volume of the congested vessels is simply a special application of this general law.

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* Boll, 'Das Princip des Wachsthums,' Berlin, 1876, p. 70.

just as little as in the case of a ring constantly worn on the finger. I also attribute, as you know, a *direct* influence having the same tendency to the compression, inasmuch as it impedes the shedding of the horny layers by pressing them together; and you will doubtless be glad to dispense with an exact explanation of the manner in which a clavus, several mm. in thickness, can cause secondary compression of the vessels of the papillary body. In the immediate neighbourhood of the corn, moreover, the papillæ are quite usually hypertrophic.

The considerable increase in size of *a spur transplanted from the foot to the comb of a cock** also depends on the greater vascularity and more plentiful flow of blood in the comb as compared with the original matrix of the spur. In like manner, the excessive growth of hair and nails, which has often been observed in connection with very vascular tumours of the extremities,† is attributable to the abnormal increase in the blood-supply. From this it is but a step to the extremely common form of *hypertrophy depending on inflammation.* I need hardly repeat that inflammatory hyperæmia has not always, or in all tissues, a stimulating effect on growth; it may often, as in muscles and glands, exert an unfavorable influence on the metabolism of nutrition. Hypertrophy depending on inflammation may be expected to occur chiefly in stratified epithelia and in the various connective tissues. Now, the existence of an inflammatory hypertrophy in the stratified epithelium of the epidermis is exemplified in many chronic skin diseases, *e.g. ichthyosis, condyloma acuminatum,* and many *warts*; in the epithelium of the mucous membranes by every chronic *catarrh of the pharynx* and more especially *of the vagina*: and with this hypertrophy there usually occurs *pari passu* an increase in the bulk of the fibrous substratum. The condition so produced is a true hypertrophy, that is, *an increase in thickness of the epithelial stratum with perfect preservation of the histological type*; for the number alone of the superimposed cell-layers is augmented. Yet a different result is certainly possible, and may often enough be met with, namely, growth of epithelium and the

* Paget, 'Lect. on Surg. Path.,' i, p. 72.

† O. Weber, 'Virch. A.,' xxix, p. 101.

formation of cell-layers in *an abnormal direction.* The skinning over of granulating wounds, &c., with epithelium is, though a favorable event, in reality a growth in an abnormal direction. But we have recently become acquainted with facts of a much more surprising character with reference to abnormal epithelial growth as the result of inflammatory hyperæmia. If a clean incision be made into the cornea of a rabbit, perpendicular to its surface, the wound, which at first gapes a little, is usually filled up by the next or following day with a perfectly transparent substance. This is not amorphous plasma; neither is it fibrin; but as H. v. Wyss* has shown—and as may easily be confirmed—it consists of the most beautiful epithelial processes, which have grown into the fissure from the anterior epithelium bordering on the wound, and which afterwards gradually disappear before the regenerating corneal tissue. The *prima intentio by epithelial proliferation* cannot, it is true, be anywhere so magnificently observed as in the cornea and lens, if for no other reason because bleeding does not here occur as a complication.† Yet the proliferation is far from peculiar to these parts; and C. Friedländer‡ has brought forward similar facts with respect to the epithelium of all possible localities. Thus nothing, according to this writer, is more common than the skinning over with epithelium of fistulæ and deeply penetrating lupous ulcers; again, in chronic subcutaneous abscesses there sometimes grows from the rete and hair-follicles an epithelial covering for the granulating internal surface of the cavity. In short, wherever epithelium abuts upon a free surface not already covered by it, it may spread itself over that surface under the influence of an inflammatory hyperæmia. Still more—after a few similar observations had been communicated from various sides,§ the author last mentioned

* H. v. Wyss, 'Virch. A.,' lxix, p. 24.

† Schuchardt, 'Z. pathologischen Anatomie d. Discisionen,' I.-D. Göttingen, 1878.

‡ C. Friedländer, 'Ueber Epithelwucherung und Krebs,' Strassburg, 1877; cf. also Zielonko, 'Med. Ctbl.,' 1873, No. 56; M. Schultze's 'Arch.,' x, p. 351.

§ Busch, 'Verhdl. d. 1ten deutsch. Chirurgencongresses,' 1872, p. 120; Cornil, 'Arch. d. phys.,' 1874, p. 270; Charcot et Gombault, ibid., 1876, pp. 272, 453; Waldeyer, 'Virch. A.,' xliii, p. 533.

called attention to the fact that in all kinds of chronic inflammatory processes involving membranes and canals covered by epithelium, abnormal epithelial processes or networks may very commonly be discovered in the inflamed and granulating connective tissue. For though it is difficult to determine whether the *atypical epithelial proliferation,* so termed by Friedländer, and by him described as occurring in elephantiasis, cirrhosis of the liver, interstitial pneumonia, &c., really leads to the penetration of epithelial processes into the granulation tissue ; or whether this appearance is not rather due to the isolation of the processes from the rest of the epithelium by the growing connective tissue; yet this uncertainty does not militate against the fact that an abnormally abundant growth of epithelium sets in in consequence of the chronic inflammation.

Many of the illustrations already given may at the same time serve as evidence for the occurrence of an *abnormal production of connective tissue* following and depending on inflammatory hyperæmia ; for in chronic catarrh of the mucous membranes the mucosa itself usually becomes thickened, and beneath a *condyloma* there is always an enlarged papilla, which in warts makes up the chief bulk of the structure. In the *mucous polypi,* which so frequently develop in the train of chronic catarrh, the proliferation of the epithelium and of the mucosa occurs simultaneously, while in elephantiasis the chronic inflammation leads to a much greater increase in bulk of the cutis and subcutaneous cellular tissue than of the epidermis. But why should I waste time in citing examples of abnormal connective-tissue growth depending on inflammation ? Have we not already determined that a new formation of vessels and connective tissue is the regular termination of every long-continuing productive inflammation, and followed out the new formation even in its morphological details ? You will therefore gladly dispense with all further discussion of the inflammatory new formation of connective tissue ; permit me only to point out that the above observations apply also to the *lymphatic glands* and *spleen.* The histological details of the chronic inflammatory affections of the lymphatic glands and spleen are, it is true, by no means so well known, as might reasonably be anticipated from their great frequency, and as

would in any case be desirable; yet it may at least be unhesitatingly affirmed that the final result of these processes is an increase in bulk of the organs with preservation of their structure, that is, a genuine *hypertrophy.*

In all the cases of the second category hitherto discussed the cause of the intensified growth could with certainty be identified as increased blood-supply, for it was everywhere possible to determine the conditions on which the latter depended, together with the modus of its development. We are not in the same favorable position with respect to some very interesting forms of hypertrophy of certain organs, of which we know only that they depend upon specific influences. I refer to the enlargement of the spleen in consequence of *intermittent fever* and to the *goitre* which is endemic in certain regions. Certain it is that neither of these conditions originates in a congenital, inherent predisposition, for they may be acquired or lost through residence in or removal from the fever- or goitre-district; nor, having regard to the rapidity with which the fever-spleen more especially develops, can it for a moment be supposed that a diminution of waste plays any noteworthy part in the enlargement of these organs respectively. There is therefore no alternative but to assume that these two hypertrophies also depend on an *abnormally abundant blood-supply,* for, as you know, with this we have exhausted the conditions of growth. But by what agency the excessive blood-supply is brought about remains unknown. Intermittent fever is a typical infective disease; hence, for reasons already familiar to you, it must be assumed that its virus is of *organised* nature. And this suggests the notion that goitre may also be produced by organisms; indeed Klebs* has attempted even to support the hypothesis by experiment, with results, it is true, which he does not himself consider convincing. Should the hypothesis nevertheless be accepted, the process would offer a certain parallel to the infective inflammations proper, with this difference, that in goitre and in fever-spleen we have to deal not with an *inflammatory change in the vessel walls,* set up by the organisms, but solely

* Klebs, 'Studien über d. Cretinismus,' Prag., 1877, p. 52; more recent experiments, attended with positive success, are mentioned by Klebs in the article "Flagellata" in Eulenburg's 'Realencyclopädie.'

with a decrease of arterial resistance in the vessels of the thyroid gland and the spleen. It is possible that a third form of specific hypertrophy of single organs or groups of organs should be classed here, namely, the *leukæmic*. At any rate we are at present unprovided with any other hypothesis to account for the origin in this affection of the enlargements of the spleen, bone-medulla and lymphatic glands—enlargements which, as is well known, may far outstrip all others in bulk. Yet the fact that the hypertrophy is complicated by the profound blood change peculiar to this disease warns us to use the greatest foresight in interpreting the entire process. Lastly, I must not omit to state that the *hyperostosis of chronic phosphorismus*, already touched upon, must on Wegner's view be classed among the hypertrophies caused by an increase, through a specific noxa, of the blood-supply.

With regard to the form assumed by the progressive disturbances of nutrition hitherto discussed, I have hardly anything to add to my former statements. Only the true hypertrophies, in the strict sense of the term, require a few supplementary remarks. By hypertrophy is to be understood *a uniform increase in the bulk of an organ in which all its constituents take part, and in which the regular form and structure of the organ are maintained.* When the volume of a lung is increased by distension of its alveoli with a liquid or solid mass, or when, through widening of its interstices, the kidney is enlarged in all its dimensions, the resulting condition is not called hypertrophy. For the establishment of hypertrophy it would be necessary that urinary tubules, vessels, glomeruli, in short, all the components of the organ, should share equally in the enlargement, so as to secure the maintenance in every single portion of the kidney of perfectly normal mutual relations between these component parts. If, then, abnormal growth of all the tissues of an organ be indispensable to the production of a true hypertrophy, it logically follows that chronic inflammation can lead only to the hypertrophy of such organs as are composed of no other tissue than connective tissue and superficial epithelium. As a fact, the majority of all the hypertrophies involving fibrous and other

connective-tissue membranes, the lymphatic glands and spleen, and the bones, have arisen on an inflammatory basis. The hypertrophies depending on diminution of waste are also confined to a few organs ; to this form the epidermis, the uterus, and the bones supply their contingent. On the other hand, there is no organ having elements capable of reproduction but may be made to undergo true hypertrophy as the result of lasting or oft-repeated arterial congestion. This applies to the spleen, to the bones, and to the other connective tissue as well as to the epithelia, to the peripheral nerves and to the thyroid body, to the muscles and glands. True, of the last two it holds good with a reservation, that *work-congestion*, but no other diminution of arterial resistance, causes muscle and gland to hypertrophy, since only the former is accompanied by that stimulation of their elements without which these organs cannot assimilate.

As to the *microscopic* appearances of hypertrophic organs the remark made on this head when discussing the atrophies is equally apposite here. Whether the enlargement of a particular organ will be effected by an increase in the size of its individual elements—Virchow's true *hypertrophy*—or by an increase in their number—Virchow's *hyperplasia*—depends on the laws of growth of the tissues in question. Thus, in all connective tissues there takes place exclusively a numerical hypertrophy, while in a hypertrophied heart, voluntary muscle, or urinary bladder, as well as in the kidneys* and liver, the muscle-fibres or gland-cells are usually more voluminous than normal. But how little fundamental importance attaches to this distinction is best taught by the never-failing presence in all considerable hypertrophies of muscular and glandular organs, of a numerical increase, or hyperplasia, as well. The same thing occurs in condylomata, where it is quite usual for a marked increase in the number of the epithelial layers to coincide with a considerable enlargement of the individual epidermic cells.

While the discussion of the importance of hypertrophy will be reserved for the chapters on the individual organs, we shall here devote a few words to the further history of the hypertrophies. The subject may be very briefly dis-

* Rosenstein, 'Virch. A.,' liii, p. 152 ; Perls, ibid., lvi, p. 305.

missed, *as the hypertrophic organs obey precisely the same laws of metabolism and nutrition as do the normal ones.* They often fall a prey to the different forms of degeneration, such as the fatty, colloid, and amyloid, to calcification, and even to necrotic processes. Nor, it is obvious, will atrophy fail to occur when the conditions favouring it exist—clearly but another way of saying that a hypertrophy may become retrogressive.

Before turning to the third class of progressive disturbances of nutrition, the tumours, it appears advisable to discuss a group of morbid processes, which, from their character, may unhesitatingly be placed in a special class of their own, namely, *the new formations of syphilis, glanders, and tuberculosis,* to which category also belong the *lupous* and *leprous processes,* and the "pearly disease" of cattle. From a purely anatomical point of view there can be no doubt that gummata and tubercles, as well as the nodules of glanders and lupus, are tumours; and Virchow* was perfectly justified in placing all these new formations under the heading of *lymphatic* and *granulation-tumours,* when classifying them according to anatomical principles. Yet on approaching them from a physiological standpoint and attempting to determine the conditions under which they originate, we at once come upon certain common characteristics, which are nowhere repeated in any of the remaining classes of neoplasms.

Of these peculiarities none is more important than their *etiology.* As for the nodules of glanders and the gummatous growths, it is absolutely certain that they are developed only when the virus of syphilis or of glanders has entered the juices of the individual affected, whether by direct transference from individual to individual, or from animal to animal, or by communication during procreation. The syphilitic and farcy tumours are therefore exquisitely *infective* products. But the same may be said of the other new formations just mentioned; so that I can only regard with approval the proposal of Klebs† to apply to the entire group the name of *infective tumours.* As regards pearly disease, it has long been

* Virchow, 'D. krankhaften Geschwülste,' ii, pp. 385, 555, Berlin, 1865.
† Klebs, 'Prag. Vierteljahrsschr.,' Bd. 126.

known to affect cattle in families and herds; and its communicability has, in addition, been recently determined by direct inoculation and by feeding.* With respect to *lepra* also, experience of the really appalling spread of the disease in localities where notoriously it had gained a footing only a few decades previously, makes it only too probable that the malady is an exquisitely *contagious* one; and although we are unacquainted with any facts going to show the contagiousness of *lupus*, its endemic occurrence in certain districts unmistakeably points to a definite virus, possibly miasmatic in character. But how is it with regard to *tuberculosis?* In coming to a decision on this question we are fortunately no longer dependent on equivocal observations on man, since pathological experiment has supplied us with a positive answer to it. Nothing could be more certain than the occurrence in certain animals—among which guinea-pigs and rabbits are the most susceptible—of death *from general tuberculosis* in six, eight, or ten weeks after the introduction beneath the skin or into the abdominal cavity of small fragments of tubercular material from the dead body of a man or from an extirpated scrofulous gland. Since Villemin's first experiments,† this result has been repeatedly verified by innumerable investigators,‡ and always with the same success. And no one who has more than once observed and examined, in the emaciated bodies of the animals, the sub-miliary eruptions in the peritoneum, pleura, kidneys, liver, spleen, bone-marrow, and choroids; further, the cheesy lymphatic glands and cheesy nodules in the lungs; will be shaken in his allegiance to this view by the doubts which from many

* Gerlach, 'Jahrb. d. Thierarzneischule z. Hannover,' 1869, p. 127; summary in 'Virch. A.,' li, p. 290.

† Villemin, 'Gaz. méd. de Paris,' 1865, No. 50; 'Gaz. hebdom.,' 1866, Nos. 42—49; 'Bull. de l'acad. de méd.,' xxxii, No. 3; 'Études sur l. tuberculeuse; preuves rationelles expér. d. s. spécificité, &c.,' Paris, 1868.

‡ Hérard et Cornil, 'La Phthisie pulmonaire,' Paris, 1867; Lebert u. Wyss, 'Virch. A.,' xl, pp. 152, 551; Klebs, ibid., xliv, p. 242; 'A. f. exper. Pathol.,' i, p. 163; Sanderson, 'Med. Times and Gaz.,' 1868, p. 431; Fox, 'Brit. Med. Journ.,' 1868, May 23; Cohnheim and Fraenkel, 'Virch. A.,' xlv, p. 216; Bernhardt, 'D. A. f. kl. Med.,' v, p. 568; Waldenburg, 'D. Tuberculose, Lungenschwindsucht u. Skrofulose,' Berlin, 1869; M. Wolff, 'Virch. A.,' lxvii, p. 234.

sides* have been thrown on the tubercular nature of the new formations. Moreover, the dispute on inoculation-tuberculosis, so energetically sustained in the second half of the seventh decade, was not concerned with the fact itself, but only and solely with its interpretation. The view then maintained by Waldenburg and others, that tubercle arises through the absorption of finely divided corpuscular particles by the blood, and their deposition in the organs, could not make any headway against the well-known facts as to the fate of injected cinnabar; though unanimity was not so soon arrived at with respect to two other diverging opinions. According to one hypothesis, that originally proposed by Villemin, and defended with special energy by Klebs, it is a thoroughly *specific* virus, inherent in tubercular products, that gives rise to tuberculosis in the inoculated animals. On the second view, tuberculosis is to be regarded as the secondary effect of an inspissated inflammatory exudation, which again, in certain animals, such as rabbits and guinea-pigs, may itself be conditioned by any foreign body selected, or even by a wound. This latter opinion I had myself adopted, in consequence of a series of experiments carried out in conjunction with B. Fränkel in the Pathological Institute of Berlin. In these experiments, guinea-pigs into whose abdominal cavity we had introduced a piece of cork, a pellet of paper, a linen thread, or other similar material, all because tuberculous. Yet the absolute failure of the experiments when repeated by myself in the Institutes of Kiel and Breslau, and by my colleague Fränkel in his private residence in Berlin, was startlingly against our conclusions; and accordingly I gladly admit the justice of the question raised by Klebs, whether an unintentional tuberculous infection of the animals experimented on may not possibly have occurred in the animal-house of the Institute in Berlin. Moreover the intestinal tuberculosis which Chauveau, Aufrecht and others† produced

* Langhans, 'Die Uebertragbarkeit der Tuberculose auf Kaninchen,' Marburg, 1867; Köster, 'Würzburg Verhandl.,' 1869, Juni; Friedländer, 'D. Ztschr. f. pr. Med.,' 1874, No. 42.

† Chauveau, 'Gaz. méd. d. Lyon,' 1868, p. 550; 'Récueil d. méd. véter.,' 1872, p. 337; 'Bull. de l'acad. de méd.,' 1874, No. 37; Aufrecht, 'Med. Ctbl.,' 1869, No. 28; Bollinger, 'A. f. exp. Pathol.,' i, p. 356; Orth, 'Virch. A.,' lxxvi, p. 217.

in rabbits and other herbivora by feeding with masses of tubercle, and the pulmonary tuberculosis acquired by Tappeiner's* dogs through repeated inhalation of powdered human phthisical sputa, could not possibly be explained on the exudation hypothesis. On the whole, in proportion as I have recently become more and more convinced of the exclusive and never-failing activity of true tuberculous material, the more certain does it appear to me that the belief of Villemin and Klebs in *the specific nature of the tuberculous virus* alone meets the facts of the case.

This opinion has been strengthened more especially by experiences, which not only gave me an opportunity of following the history of inoculation-tuberculosis directly with my own eyes, but made clear the analogy of the tuberculous virus with that of glanders and syphilis in one important point.† Of the two latter affections we know that they, like all other infective diseases, have an incubution stage which in acute glanders lasts from three to eight days, and in syphilis from three to four weeks. In order to arrive at certainty on this point for inoculation-tuberculosis, the simplest method appeared to be the introduction of the material into the *anterior chamber of the eye.* A particle of tuberculous material from a body recently dead, or still better from an extirpated caseous lymphatic gland, of about a cubic millimetre in size, and carefully cleansed, when cautiously introduced by a linear incision behind the cornea of a rabbit, causes as a rule but a slight iritis and keratitis, which may be completely controlled by dropping in atropine. After a few days the cornea is perfectly clear, the iris absolutely unclouded and normal in condition, nor can any flakes be discovered in the humor aqueus, so that the implanted particle may be seen with sharp and clearly defined contour upon the capsule of the lens. These appearances remain unaltered for several weeks, or there is at most a slight diminution in the size of the caseous particle. But between the twentieth and thirtieth day, in all the cases observed by us, the scene is suddenly changed; in the tissue of the iris a considerable

* Tappeiner, 'Virch. A.,' lxxiv, p. 393.

† Cohnheim u. Salomonsen, 'Stzgsb. d. Schles. Gesellsch. f. vaterländ. Cultur.,' 13 Juli, 1877; Salomonsen, 'Nord. med. Arkiv.,' xi, 1879.

number of small transparent greyish nodules make their appearance; they project slightly into the anterior chamber, and between them the iris itself is intensely *reddened* and blurred. During the next few days the small nodules multiply, while some grow to be nearly a millimetre in diameter. This condition may in some eyes remain stationary for weeks, but in others the iritis becomes complicated by a severe keratitis vasculosa with keratomalacia; and in some animals the eyes are destroyed with the signs of panophthalmitis. But the chief point of interest is the common, though not invariable, occurrence of *a more or less extensive tuberculosis of the lungs, lymphatic glands, spleen, and other organs.* From these experiments it may undoubtedly be inferred: first, that inoculation-tuberculosis may develop *without the intermediate stage of inspissated exudation;* and, second, that it has a period of incubation, which in the rabbit amounts on the average to twenty-five days. In other species, as the guinea-pig, it appears, we may say in passing, to be shorter by a week.

With such positive and easily repeated experiments before us, it should apparently be impossible still to discuss or discredit the infectiveness of tuberculosis. True it is only a short time since we first learned that it is communicable; and you have of course no doubt that the causes of this most destructive of diseases were long before this persistently sought after. It was formerly assumed—and there are still some writers who cannot abandon these views*—that tuberculosis develops spontaneously, or is conditioned by ordinary irritants, atmospheric, traumatic, or other; but only in such individuals as are specially predisposed to it, either through inheritance, antecedent disease, poor nourishment, or other unfavorable hygienic conditions. This predisposition was located in the vessels and tissues, which were said to be more than usually *irritable* or *vulnerable,* and would more readily react with inflammation to noxæ of all sorts, while the inflammation thus set up would be difficult and slow of resolution.† The exudations would therefore remain where

* Geigel, 'D. A. f. klin. Med.,' xxv, p. 259.

† Virchow, 'Geschwülste,' ii, p. 588; Buhl, 'Lungenentzündung, Tuberculose u. Schwindsucht,' München, 1872, p. 111; Hueter, 'Allg. Chirurgie,' p. 730; Wagner, 'Hdb.,' p. 625.

thrown out, and become inspissated; the lymphatics and glands would be implicated in the inflammatory process, and in the glands would be formed the well-known cheesy foci, which have for ages been regarded as the criterion of *scrofula*. These caseous foci would then be the source of the tuberculous infection proper; though it was maintained by certain writers, among others by Virchow, that in persons predisposed to tubercle, the disease might also develop directly in consequence of local irritation without any such caseous intermediate stage. But by tuberculous infection was meant, not the idea so familiar to us of a virus arriving in the body from without, but an *auto-infection* of the organism from these caseous inspissated foci.* That the scrofulous inflammations and the tuberculous products are peculiar was and is to-day recognised by the opponents of the theory of a specific tubercular virus; but they find in the disposition of the organism that peculiar character which the advocates of the theory suppose to be inherent in the nature of the virus itself.

Now that we know tuberculosis to be communicable, the idea of a constitutional anomaly cannot, in my opinion, be any longer maintained. Or are we to believe that the human organism has the power of producing within itself *a material possessing all the properties of a true infective virus*, a material capable of reproducing itself, and even of being transferred to other species without losing its activity? On the other hand, by unreservedly and logically taking up a position on the side of the theory of infection, not only do all essential difficulties disappear, but a large number of long-known facts become at one intelligible and are seen in a clearer light than before.† Many of the difficulties were indeed self-created, chiefly in order that the hypothesis of a *predisposition* or *disposition to tuberculosis* might be set up and maintained. And indeed, were it really established that every extension of bronchitis, every inflammation of the lungs, however originating, could become the starting-point of a tuberculosis, one would be perfectly justified in assuming that the individuals

* Cf. Buhl, 'Zeitschr. f. ration. Med.,' N. F., viii, p. 49, 1857.

† Cf. Cohnheim, 'D. Tuberculose v. Standpunkt d. Infectionslehre,' 2 Aufl., Leipzig, 1881.

in whom these inflammations run such a malignant course, instead of the usual incomparably more benign one, have a peculiar constitution, and are, in short, predisposed to a catastrophe of the kind. But it is not so in reality. When a pleuritic effusion fails to be resorbed, and becomes chronic or recurs, and unmistakeable signs of pulmonary tuberculosis afterwards manifest themselves, this is because the pleurisy was *from the first* tubercular. The same may be said of bronchitis, pneumonia, and of swelling of the lymphatic glands: caseation sets in because the affections were from the start called forth by the tuberculous, or as it is called here, scrofulous poison. No less doubtful is the second argument, usually placed in the forefront of the battle by the upholders of the theory of a tuberculous predisposition, namely *inheritance* of the disease from the parents by the children. Were the inheritance genuine, in the sense that the children of tuberculous parents come into the world with tuberculosis, as happens only too often in syphilis, the congenital tuberculosis would not go to prove the assumed predisposition real. Meanwhile, well-accredited cases of genuine congenital tuberculosis are extremely rare;* and so distinctively is tuberculosis a disease of extra-uterine life that even in tuberculous families the great majority of persons do not fall a sacrifice to the malady till several years have elapsed, very many of them not till puberty is passed and after a childhood free from disease. But does it really follow from this that in these cases the *disposition to, the foundation of, tuberculosis is inherited*, though not the tuberculosis itself? On the contrary, the rare yet positively observed cases of congenital tuberculosis clearly favour the view adopted by us—that tuberculosis is an infective disease, the specific virus of which may, like that of syphilis, be communicated from parent to child. The assumption of an inherited predisposition to this disease is not in my opinion necessary to explain its subsequent development in the children of tuberculous parents.

* Scanzoni, 'Lehr d. Geburtshülfe,' 1855, p. 422; Rilliet et Barthez, 'Maladies des enfants,' 2me éd., iii, p. 404; Charrin, 'Leçon méd.,' 1873, No. 14, ref. in Virch.-Hirsch's 'Jahresb.,' v, 1873, i, p. 247; possibly some of the cases, a brief mention of which is made in 'Arch. der Kinderheilkunde,' ii, p. 345, should be placed here.

For the fact that several members of a family become tuberculous, proves nothing but the presence in it of conditions calculated to give rise to tuberculosis; and what condition could be more favorable to its production than the presence of a phthisical patient in the family? When a child nourished by its tuberculous mother becomes tuberculous, it is less far-fetched to assume the communication of the disease by the mother's milk, into which the virus may pass, than the inheritance of a diseased constitution.* Besides, in how many instances is the malady acquired through inhaling the dust of dried phthisical sputa from a member of the family! In short, where the opportunities for acquiring tuberculosis are so manifold, we must be furnished with proofs of at least a different character to those already brought forward before we can accept as demonstrated the existence of an hereditary predisposition to the disease.

How greatly our conception of the entire disease is aided by the theory of infection can, as already stated, be perceived only by him who estimates in the light of this doctrine the clinical and pathologico-anatomical knowledge previously accumulated. Here may be mentioned, for example, the frequently observed *epidemic* occurrence of general miliary tuberculosis, to which attention was long ago directed by Virchow.† Still more important are the cases of direct communication of the disease, especially amongst the married, which though often talked about, are for obvious reasons difficult to prove.‡ But by far the most interesting result of the doctrine of infection, is the light thrown by it on the *anatomical distribution* of tuberculosis. For though since Laennec, all pathologists have been much struck by the suggestive resemblance of the course run by tuberculosis to that of the infective inflammations,§ it was not possible, till this more modern stand-

* Epstein, 'Prager Vierteljahrsschr.,' 1879, N. F., ii, p. 103.

† Virchow, 'Med. Reform,' 1849, No. 49; 'Würzb. Verhdl.,' iii, p. 104.

‡ Villemin, 'Union méd.,' 1868, No. 12; Drysdale, 'Brit. Med. Journ.,' 1868, Feb. 1; J. Petersen, 'Lungenswindsot og Tubercul. omtwist. contagiosited og Inoculabilitet,' Kjobenhavn, 1869; H. Weber, 'Transact. of the Clin. Soc. of London,' 1874, vii; Musgrave Clay, 'Étude sur l. contagiosité de la phthise pulmonaire,' Paris, 1879.

§ Laennec, 'Traité de l'auscultation médiate,' i, ii; Virchow, 'Geschwülste,' ii, p. 721.

point was attained, to perceive in this resemblance a necessary agreement, and not a mere external and in a measure accidental analogy.* The distribution of the disease throughout the body is first of all determined by the *point of entrance* of the virus. When, as happens in the vast majority of cases, the poison enters the organism with the inspired air, the disease will commence in the lungs, and will from them be propagated to the bronchial glands and pleuræ; disease of the larger air-passages, larynx and trachea, commonly follows, while the alimentary canal may become affected, no doubt by the swallowing of the infective sputa. Or the tuberculosis attacks in the first instance the alimentary canal, and then gradually spreads to the mesenteric glands and peritoneum, whence it may extend to the spleen and especially the liver, and occasionally in females to the fallopian tubes and the uterus. But it may proceed in an opposite direction, *i. e.* primary tuberculosis of the genitals may be followed by a secondary affection of the peritoneum; and while the disease often progresses from the kidneys to the ureters, by them to the bladder and prostate, then to the vesiculæ seminales and vasa deferentia, ultimately to the epididymis and testicle, it no less frequently takes the contrary course and passes from the testicle to the kidneys. Its distribution is next determined by the transport of the virus by the blood-stream, which, when the quantity removed in a short time is large, gives rise to acute general miliary tuberculosis,† while it otherwise leads to localisation of the tuberculous process in regions far removed from the point of entrance, to the characteristic *fungous arthritis*‡ for example, which was long erroneously supposed to be perfectly distinct from true tuberculosis and therefore received the name "local tuberculosis" —a misleading term which has consequently been abandoned.

All these facts speak, as I think, so eloquently and pointedly for the *infective nature of tuberculosis*, that we cannot allow ourselves to be shaken in our conviction by the circum-

* Klebs, 'Virch. A.,' xliv, p. 242; Cohnheim, 'Die Tuberculose, &c.'

† Cf. Weigert, 'Virch. A.,' lxxvii, p. 269.

‡ Köster, 'Virch. A.,' xlviii, p. 95; 'Med. Ctbl.,' 1873, No. 58; Friedländer, ibid., 1872, p. 673; 'Volkmann'sche Vorträge,' No. 64; on the contrary, König, 'D. Ztschr. f. Chir.,' xi, p. 531.

stance that the direct demonstration of the tuberculous virus is still an unsolved problem.* Not till its solution has been accomplished will many unexplained details in the course of the disease become intelligible. We shall then, moreover, be in a position to answer the important question whether the virus is associated with the actual tuberculous products alone, or, as indicated by the more recent experiments of Baumgarten,† also exists, though perhaps only temporarily, in the juices of the affected individual, more especially in the blood. We may also perhaps discover why the virus fixes upon one individual more readily than upon another, and why it more easily and rapidly develops in some than in others. These are indeed more or less lamentable gaps in our knowledge of tuberculosis, yet only such as are likewise to be met with in but too many of the infective diseases. Was I not obliged to confess with regard to the majority of these maladies that we are not yet in a position to demonstrate their specific organisms? And, at any rate, we are no worse off here than in the case of syphilis,‡ the infective character of which is doubted by no one. In only one of the diseases now engaging our attention has this desideratum been met in a manner scientifically unassailable—namely, in lepra, in the nodules of which, as I have already told you, Neisser§ has invariably found a *bacillus* having a characteristic shape and distribution. Though this is at present a solitary discovery, we greet it with all the more pleasure, as it is calculated to strengthen our hopes of similar discoveries in the remaining infective tumours, presenting as these do so many points of resemblance with lepra.

For to the etiological resemblance of the new formations with which we have been engaged, must be added a similarity *in anatomical structure* and in *history*. The cellular elements composing them present, while the growth is recent, such a perfect likeness to white blood-corpuscles that the second

* A short sketch of organisms found in tuberculosis was given by Klebs at the 'Naturforscherversammlung,' in Munich, 1877, Tageblatt, p. 274.

† Baumgarten, 'Med. Ctbl.,' 1881, No. 15.

‡ Cf. Klebs, 'A. f. exper. Path.,' x, p. 161.

§ Neisser, 'Bresl. ärztl. Zeitschr.,' 1879, Nos. 20, 21; 'Virch. A.,' lxxxiv, p. 514.

name proposed by Klebs,* *leucocytomata*, seems no less appropriate than, from an etiological standpoint, does that of infective tumours. Besides the lymphoid, there is present a variable number of large epithelioid, cells—in the interior of which in lepra most of the bacilli are situated†—and usually a few *giant-cells*, each having several nuclei, the majority lying towards the periphery of the cell.‡ The combination of these different elements to form *small nodules* is specially characteristic of many of the infective tumours. The elements are usually arranged in the nodule as follows: in the centre or more excentrically there lies one, or more rarely two or three, giant-cells; the giant-cell is immediately surrounded by epithelioid cells; the remainder of the nodule consists exclusively of cells resembling leucocytes, which gradually become lost in the normal tissue of the neighbourhood. The formation of nodules is most typical in tuberculosis—hence its name; yet lupus also has usually a similar appearance, and very beautiful examples of nodules may be seen in certain varieties of syphilis. The individual nodules do not as a rule increase very much in size, but the coalescence of several of them to form larger ones is common, and in this way very bulky flat or globular patches may arise. It would, however, be erroneous to assume that all the larger nodules in tuberculosis originate merely by confluence; many, I have no doubt, of the so-called solitary tubercles of the brain, as well as of the larger tubercular nodules in the spleen, liver, &c., have been formed by the direct growth of smaller ones. But in no case is the production of small nodules to be regarded as a general characteristic of the infective tumours. Not only is there a decided preponderance of large nodules

* Klebs, 'Prag. Vierteljahrsschr.,' Bd. 126.

† Neisser, 'Bresl. ärztl. Zeitschr.,' 1879, Nos. 20, 21; 'Virch. A.,' lxxxiv, p. 514.

‡ Virchow, 'Geschwülste,' ii, p. 635; Langhans, 'Virch. A.,' xlii, p. 382; Klebs, ibid., xliv, p. 242; Brodowski, ibid., lxiii, p. 113; Hering, 'Histolog. u. experim. Studien über Tuberculose,' Berlin, 1873; Schüppel, 'Untersuchungen über Lymphdrüsentuberculose,' Tübingen, 1871; Thoma, 'Virch. A.,' lvii, p. 455; Friedländer, ibid., lx, p. 15; 'Volkmann'sche Vorträge,' No. 64; J. Arnold, 'Virch. A.,' lxxxii, p. 376, lxxxiii, p. 289; Baumgarten, ibid., lxxxii, p. 397; Ziegler, 'Experiment. Untersuchungen über d. Herkunft d. Tuberkelelemente, &c.,' Würzburg, 1875; 'Volkmann'sche Vorträge,' No. 151.

in the tuberculosis of many animals, as, for example, the ape, but these are distinctly the rule in "pearly disease," lepra, and the ordinary gummata of syphilis. Rather we might single out, as a peculiarity common to most of the infective tumours, the occurrence in them sooner or later of *necrotic processes.* The tendency to necrosis may have a certain connection with the very imperfect blood-supply of these tumours; and this view is clearly supported by the late occurrence of necrotic changes in leprous new formations, which not only contain vessels but are by no means poorly supplied with them. Still we shall not go far astray, if we attribute the necrosis principally to the action of the same virus, to which the infective new formation itself is due.

These are the main anatomical features of the infective tumours, as shown by their renewed examination. True, in matters of detail they present many points of dissimilarity. This applies especially to their situation. *Tuberculosis* and *scrofula* evince a preference for the entire lymphatic apparatus, and next for the lungs, the liver, the urinary organs, the bone-medulla, the serous membranes, &c.; while *syphilis* selects above all the *orifices* of the body, further certain mucous membranes, and lastly the skeleton, the liver, and the testicles. *Glanders* also prefers the mucous membranes, and affects the lymphatic glands, the muscles, the lungs. *Lupus* attacks the skin; "*pearly disease*" the serous membranes; and *leprosy* the skin and subcutaneous tissue, as well as many of the internal organs. There is, further, a difference in the form assumed by the necrotic processes. *Caseation* is strictly pathognomonic of tuberculosis, though the necrosis of syphilitic gummata has a close resemblance to it; on the other hand, glanders is characterised by the formation of a *tenacious mucous mass,* and pearly disease by the very opposite of this—*calcification.* In both mucous membranes and skin, ulcers are developed as a result of the necrotic process. In tuberculosis the ulceration is chiefly met with in the mucous membrane of the respiratory, digestive, and genito-urinary systems; in syphilis it is found in the skin, mouth and pharynx, rectum and vagina, nose and larynx, &c.; in lupus in the skin; in glanders in the nose. When the ulcers heal or the new formation is resorbed, deep radiating cicatrices

with loss of substance always remain. But whether healing occurs, does not so much depend on the anatomical structure of the tumour or ulcer as on the nature of the disease. Universal experience has taught that syphilis, lupus, and to some extent lepra may, and ordinarily do, become retrograde; while the prognosis is bad in most cases of tuberculosis, glanders, and pearly disease.

These few hints will suffice to show that though the infective tumours differ in their essential nature, they are closely related in anatomical characters and history. By employing the criteria laid down by medicine and pathological anatomy it is usually possible to make during life as well as post mortem a certain differential diagnosis between syphilis, tuberculosis, glanders, lupus, &c. But every experienced physician and pathological anatomist has seen cases, which the more carefully they investigated them, the more they were inclined to vacillate in their opinion, till in the end they could by the naked eye arrive at no more than a probable diagnosis. The microscope also, if resorted to in these cases, not uncommonly leaves us in the lurch. For under the microscope, the leucocytes, epithelioid, and giant-cells of tubercle have precisely the same appearance as those of lupus or a syphilitic gumma; while in necrotic parts the differences are much more striking when examined by the naked eye than under the microscope. In many instances of caseous salpingitis and pericarditis, our search after a precise indication of the original tubercles, by the coalescence of which the caseous masses have arisen, will be no more successful than would be a similar undertaking in the periphery of a gumma of the liver.

There remains a third point of similarity between the infective tumours, sharply distinguishing them from all other neoplasms, namely, their *intimate relation to inflammation.* Inflammation is a very frequent accompaniment of the infective new formations, and may take the productive, fibrinopurulent, or, not rarely, the hæmorrhagic form. A gumma is almost invariably surrounded by dense inflammatory connective tissue; tuberculosis of the serous membranes is usually complicated by fibrinous or hæmorrhagic inflammation; and the mucous membrane about a nodule of glanders is

always in a condition of intense purulent catarrh. It is impossible to determine whether there is in these cases a direct relationship of dependence—whether the nodules may have originated in the inflammatory products, or the inflammation have arisen in the train of, and in dependence on, the nodules. The relationship rather appears to be that both—new formation and inflammation—are *co-effects of the same cause.* The most striking evidence for this belief is furnished in my opinion by the occurrence in these diseases of perfectly analogous inflammations, in which, though conditioned by the causes at the root of the general affection, *the new formation is completely absent.* I may remind you of the syphilitic inflammations of the skin, periosteum, liver, and many other organs; of the intermuscular abscesses and the purulent osteomyelitis of glanders; of lupus erythematosus; and above all of the large class of so-called scrofulous inflammations of the skin, mucous membranes, and lymphatic glands, to which must be added *caseous pneumonia.* Possibly, as pathological histology progresses, we may discover some characters serving definitely to distinguish the products of these from that of ordinary inflammation (as has already been attempted with reference to scrofulous inflammation of the lymphatic glands);* but it is improbable that the view, according to which these processes are inflammatory in their nature, will in any wise be altered.

The group of new formations, which, following Klebs's example, we have placed together under the name *infective tumours,* and distinguished from other neoplasms by reason of the peculiarities above described, is, I think, a clearly defined one. And obviously this classification would not suffer, should it hereafter be found that the circle of diseases included in the group should be drawn in some other way. Two possibilities are open; either that the number of affections embraced in our list must be reduced owing to our having classed as distinct diseases some which have no claim to such a position, or that it must be increased, inasmuch as more accurate research may result in the placing among the infective tumours of conditions previously unknown or included in other groups. As regards the former alternative, the ex-

* Schüppel, l. c.

perimental investigations of the last ten years have made it more and more probable that *tuberculosis* and *pearly disease* are not simply nearly related affections but *the product of one and the same virus.* This result is due to the varied experiments of Gerlach,* Klebs,† Bollinger,‡ Chauveau,§ Orth,|| and others, who, by inoculating and feeding with material derived from the pearly disease of cattle, as well as by administering milk from cows affected with it, produced in different animals, most easily in herbivora, a tuberculosis identical with that obtained by employing tuberculous or scrofulous material from the human subject. Indeed, the effects of inoculation with small particles of the pearly material into the anterior chamber of the eye differ in no respect, as Baumgarten¶ has shown, from those following the introduction of tuberculous products; an inoculation stage is followed by tubercle of the iris and then by general tuberculosis. As against these results, it would not signify much were the anatomical and histological differences between human tuberculosis and that of cattle much more important than they really are. But as a matter of fact the chief distinction is merely the speedy and abundant infiltration of the necrotic tissues in cattle with lime-salts, a change which in man is usually slight and limited in extent, and the cause of which must certainly be looked for in the very different diet in the two cases. While then the pearly disease of cattle, regarded as an independent and distinct affection, should be removed from our list of diseases, it appears to me, on the other hand, no less justifiable to include another disease in the group of infective tumours, namely, *actinomycosis.* I have spoken on a former occasion (vol. i, p. 329) of this disease, but only to state that the characteristic *ray fungus* has repeatedly been detected in suppurating phlegmon in man.** Yet this was not sufficient to characterise the actinomycotic products even in the human subject—in

* Gerlach, 'Jahrb. d. Thierarzneischule z. Hanover,' 1869, p. 127, summary in 'Virch. A.,' li, p. 290.

† Klebs, 'A. f. exper. Path.,' i, p. 163.

‡ Bollinger, ibid., p. 356.

§ Chauveau, 'Recueil d. méd. vét.,' 1872, p. 337.

|| Orth, 'Virch. A.,' lxxvi, p. 217.

¶ Baumgarten, 'Berl. klin. Wochenschr.,' 1880, Nos. 49, 50.

** For literature see note ‡, vol. i, p. 329.

whom the accumulations of pus are usually surrounded by lax granulation-tissue—still less so in cattle, where the formation of a dense and mostly somewhat firm granulation-tissue is so prominent a feature that the malady, which in these animals almost always commences on the jaws or in the mouth, was formerly termed *maxillary sarcoma*, and *bone cancer.* We accordingly find in actinomycosis all the essential criteria, so far as I can judge, which we determined were characteristic of the infective tumours. Thus it presents itself as new-formed tumour-like masses, which resemble so-called granulation-tissue in that they consist of lymphoid and epithelioid, as well as giant-cells—the constituents, that is, which go to compose the leucocytomata of Klebs. Moreover, these tumours result from the action of an infective virus, the actinomyces, by the introduction of which into the abdominal cavity of calves Johne* has recently succeeded in directly producing the disease. And lastly, the affection is so closely related to the true inflammations that more or less extensive suppuration is invariably associated with the harder nodules. It may be also that an additional form—in this case from the group of true tumours—should be placed among the infective granulomata now occupying our attention, namely, *lymphosarcoma.* On the ground of histological structure there would of course be no objection to such a classification, since the lymphosarcomas are constructed on the type of the leucocytomata. Besides, every surgeon knows how frequently inflammation sets in in the neighbourhood of a lymphosarcomatous packet of glands. But with reference to the decisive point, its infective etiology, I should like to remind you of the facts ascertained in Schneeberg with regard to the lung disease of the miners there.† In Schneeberg, everyone who had for a number of years descended the cobalt mines, developed without exception new formations in the lungs, which were at first held to be cancers till Wagner identified them as lymphosarcomata. The nodules grow slowly, but may attain considerable dimensions; they may also spread

* Johne, 'D. Ztschr. f. Thiermedicin,' vii, p. 141.

† Hesse, 'A. d. Heilkunde,' xix, p. 160, with postscript by E. Wagner Härting u. Hesse, 'Eulenberg's Vierteljahrrschr.,' xxx, p. 296, xxxi, pp. 102, 313.

from the lungs to the lymphatic glands and pleuræ, or even to the liver and spleen, just as do the malignant tumours; and in the end the affected individual perishes from gradually increasing marasmus. Notice carefully that the other inhabitants of Schneeberg, who do not enter the mines, never develop the characteristic tumours! Yet it cannot for a moment be supposed that the cobalt, nickel, or bismuth—in short the metals there manipulated—could give rise to the tumours; if for no other reason because the disease is completely unknown in similar mines, for instance, in the south of Sweden. Is there not then a certain probability that a poison of a very different kind, an organised one, contained perhaps in the water of some one or other of the pits, may be the cause of the lymphosarcomatosis? Such an assumption would thoroughly accord with the trustworthy observations which prove that lymphosarcoma may become retrograde under the influence of arsenic.* That a true tumour or growth should disappear on the internal administration of remedies is a thing unknown to exact medical science, while the history of syphilitic products shows vividly enough that against the infective tumours internal medicine is fortunately not so impotent. Hence there appears to me to be some justification for raising the question, whether *part* of the new formations now classed together under the name lymphosarcoma should not be placed among the infective tumours; for that these considerations apply to all lymphosarcomata is a notion to which for the present I am unwilling to subscribe.

But whether the circle of infective tumours be made to embrace few or many varieties, it is unfortunately true of all of them that as regards the detailed history of their development we are very imperfectly informed. We know that a tubercle of the choroid may develop within twenty-four hours to such a size as to be clearly recognisable by the ophthalmoscope, and we have long had sufficient experience of the rapid growth of lupous and syphilitic nodules. Yet we know nothing whatever of their actual mode of growth; and in particular we are ignorant on the one fundamental point, an acquaintance with which is evidently necessary

* Israel, 'Berl. klin. Wochenschr.,' 1880, No. 52, where earlier observations are also recorded.

before we can proceed further—I mean *the source of the cellular elements of these new formations.* For we must not conceal from ourselves that not one of the many hypotheses, most of them based on the histological structure of the spot in which the tumour arises, has done more than establish a certain amount of probability in favour of one view rather than another; and we have no proof that the cells of these tumours are derived from the endothelium of the lymphatics,* or from the cells of the adventitia of the vessels,† or from the fixed or the wandering cells of connective tissue.‡ On the other hand, if due weight be given to the intimate relations subsisting between all these affections and the inflammatory processes, the idea must almost involuntarily force itself upon one that the leucocytes of the infective granulation-tumours, like those of true inflammatory granulations, are in the last instance *emigrated colourless blood-corpuscles.* But though this assumption is highly seductive, and though all the morphological details of the development of the infective tumours may be easily explained by its aid, not a particle of actual evidence is as yet forthcoming in its favour; so that it is reserved for pathological histology and the history of development to decide, in their further progress, whether the infective tumours should be classed rather with the infective inflammations than with the infective hypertrophies, or whether some intermediate position of unknown nature should be reserved for them.§

* Klebs, Köster, ll. cc.

† Deichler, Beitr. z. Histol. d. Lungengeweb.,' Göttingen, 1861; Colberg, 'D. A. f. klin. Med.,' ii, p. 453; 'A. f. Ophthal.,' ix, 3, p. 140; Bastian, 'Edinb. Med. Journ.,' 1867, p. 875; Aufrecht, 'Med. Ctbl.,' 1869, p. 433 (Adventitia of lymphatics); G. Armauer Hansen, 'Bidrag hil Lymfekertlenes, &c.,' Christiania, 1869, ref. in Virch.-Hirsch's 'Jahresber. f. 1871,' i, p. 156.

‡ Virchow, 'Geschwülste, ii, p. 638; Busch, 'Virch. A.,' xxxvi, p. 448; Cohnheim, ibid., xxxix, p. 49.

§ On the subject of this chapter consult further Virchow, 'Cellularpathologie,' 4 Aufl., p. 482; 'Handb.,' i, p. 326; C. O. Weber, in Pitha-Billroth's 'Handb.,' i, pp. 240–285; Wagner, 'Handb.,' p. 485; Billroth, 'Allg. chir. Pathologie und Therapie;' Ziegler, Perls, &c.

CHAPTER VII.

TUMOURS.

Laws regulating the growth of the genitals, and in particular of the gravid uterus.—Monstra per excessum.—General hypertrophy.

Retention tumours.—Classification of new growths.—Definition of a new growth.

Etiology of tumours.—Refutation of the traumatic and infective theories of causation.—Embryonic germs.—Experiments.—Heredity.—Congenital occurrence.—Relation of the congenital rudiment to the development and growth of the tumour.—The localisation of the tumours explained on the hypothesis of embryonic germs.—Situation of the cancers.—Myomas of the uterus.—Adenomyomas of the prostate.—Adenoma of the mamma.—Heterologous tumours.—The constitution and structure of tumours explained on the embryonic theory.—Morphological atypia.—Histological likeness and unlikeness to the matrix.—Embryonic form of the tumour-elements.—Myxoma.—Sarcoma.

Relation of tumours to hypertrophy, illustrated by goitre and lymphoma, and to inflammatory new formations.

Biology of tumours.—No work done by them.—Conditions of their growth.—Their metabolism and nutrition.—Their atypical vascularisation.—Circulatory disturbance and degeneration in tumours.—Necrosis and ulceration.

Further history of tumours.—Their persistence.—Central and peripheral growth.—Circumscribed and diffuse limitation.—Their growth held in check by the tissues in their vicinity.

Benign and malignant neoplasms.—Their criteria.—Carcinoma and sarcoma.—Generalisation of benign tumours.—History of the generalisation.—Generalisation by means of the lymph-stream.—Metastases proper.—Agreement in

structure of the secondary with the primary tumour.—Rejection of the theory of infection of the juices.—Transport of tumour-elements.—Physiological resistance of the normal tissues.—Lost in consequence of inflammation, old age, predisposition, either inherited or acquired in an unknown manner.—Ulcus rodens.—Chimney-sweeps' and paraffin cancer.—History of growth of glandular cancer.—Conditions of malignancy in the tumours.—Benign and malignant lymphomas.—Causes of localisation of metastases.

Infectiveness of the malignant tumours as compared with that of the infective inflammations and infective tumours.

Importance of tumours for the organism.—Local disturbance.—Every tumour deprives the body of a quantity of highly organised material.—Danger attending the rapid growth of tumours.—Destruction of normal tissue by their growth.—Dangers of necroses.—Secondary cachexia.

HAVING discussed the progressive derangements of nutrition which depend upon a diminution of consumption and upon an increase of the blood-supply, we now come to the third and last of the possible groups, that based on *an inherent disposition.* The last of the possible groups, we may venture to call it, bearing in mind the general laws of growth. But do progressive disturbances of nutrition, whose cause is to be sought in the original disposition of the germ, really exist? Yes, there are such; and you will shortly learn that they, in my opinion, play an extremely important *rôle* in pathology. But before attempting to enter into a detailed explanation, permit me to illustrate my meaning by a couple of examples, drawn partly from the normal, partly from the pathological development of man.

With the object of elucidating the influence of the original germinal material on the physiological growth of the human body, I have repeatedly referred to the history of the *genitals.* For only in consequence of organisation, that is, of the original disposition of the germ, does the growth of the genitals during childhood simply keep pace with, or even lag behind, that of the remainder of the body, and then suddenly become greatly accelerated and increased. Here you have

a growth, determined by the disposition of the germ, and yet one which, when estimated by that occurring during childhood, is beyond doubt *abnormal*, and only escapes being pathological for the reason that the growth of the child is, according to the type of our organisation, normal but for a definite period. But the history of the genitals offers a still more striking example of abnormal growth, depending on inherent disposition, *in the enlargement of the uterus during pregnancy*. For, if asked what is the cause of the increased growth of the pregnant uterus, it is far from sufficient to point to the augmented supply of arterial blood determined by the developing ovum. We know that the muscle-fibres of an adult assimilate only when stimulated, *i. e.* when doing work ; the musculature of the urinary bladder or of the stomach increases in bulk only when abnormal obstacles excite to more energetic contraction. The pregnant uterus, whose office is anything rather than contraction, nevertheless acquires in a comparatively short time dimensions many times greater than the original; its muscle-fibres become enormously elongated and thickened, and also increase in numbers. The hypertrophy of the gravid uterus cannot therefore be compared to the increase of the muscles during work, but only and solely to the enlargement which every part of the body, including the muscles, undergoes during the proper growing period. But this is equivalent to saying that in consequence of a disposition inherent in the germ of mammals and man, the uterus in certain circumstances, namely, after impregnation, grows till it considerably exceeds its ordinary dimensions. The participation of the nervous system in this process is limited, in that at most it helps to regulate the amount of arterial blood-supply ; and we learn in how great a degree the blood-supply of the gravid uterus is independent of the nervous system from the many observations of regularly developed pregnancy in women who were completely paralysed in consequence of the presence of a focus of disease above the lumbar region of the cord, but especially from the interesting experiments of Goltz,* who observed a perfectly regular gestation in bitches after destruction of its lumbar portion. The growth of the uterine vessels keeps pace with

* Goltz, 'Pflüg. A.,' ix, p. 552.

that of the other tissues of the organ, just as do the vessels of all parts during the growing period; and this process, repeated in every succeeding pregnancy, accordingly offers a most instructive example of a growth depending on the original disposition of the germ, which is, at any rate, *exceptional*, and which we term normal merely because it is established in the type of our organisation.

By morbid embryology the entire class of *monstra per excessum* is, it is well known, explained by supposing an abnormality of the embryonic germinal material. Nor can I imagine any more plausible explanation for all the forms of duplicity, from the production of complete double monsters down to polydactylism, than that which refers them to the redundant formation and multiplication—leading to reduplication—of a larger or smaller portion of the earliest primitive embryonic cells arising by fission.* That these are really examples of abnormal growth depending on the original disposition of the germ will at any rate not be disputed. But should you object that in these cases the individuals are born with the abnormality, and that consequently the condition is not one of genuine pathological growth; I answer, first, that I am unable to recognise any fundamental difference between fœtal and extra-uterine growth, and second that I can adduce examples of extra-uterine abnormal growth depending on embryonic causes. It is known of so-called *giants*, that some come into the world as unusually large children; here, it may be said, an originally large germ had subsequently developed in the same proportions. It has, however, no less often been determined that those who afterwards become giants are at birth not at all above the average size of new-born children; and that the enormous growth had begun after birth—sometimes a considerable time, even months or years, afterwards. True we know too little of the details of growth of the different tissues to enable us to state in what consists the abnormality of the germinal matter in these cases; but, however we may picture it to ourselves, the development of a child of normal size into a giant must of necessity depend upon properties inherent in the germ. Still more instructive, as I think, are the remark-

* Cf. Panum, 'Virch. A.,' lxxii, p. 165.

able cases of *hypertrophy* of one or more extremities, a number of which are described in the literature.* In some of the individuals in question, an inequality of the arms or legs could already be detected at birth; yet Friedberg,† whose careful and prolonged observation of a case of this kind allowed of his determining by measurement that the growth of the right or hypertrophied leg continued for years to exceed that of the left in all dimensions, thus showed that the hypertrophy was, as he expresses it, not merely a congenital, but a *progressive* one. Think of those still more decisive cases,‡ where not the slightest difference is for years apparent in the size of the opposite extremities, till one leg or one arm more or less rapidly begins to grow with much greater vigour than its fellow, and its constituent parts—bones, muscles, fat, skin, &c.—now attain colossal dimensions! Even if the absence of every recognisable external cause were not more than sufficiently testified to in the majority of these cases, I think you would not doubt for a moment that the abnormal growth is here caused solely by irregularity in the germinal material.

There is, you perceive, nothing mystical in the view that the disposition of the germ is one of the causes of excessive growth; that it is so both in the physiological growth of the genitals at puberty, and of the uterus during pregnancy, as well as in the pathological development of the *monstra per excessum*, the duplicities, and the complete or partial congenital hypertrophies. This is a view, besides, that will scarcely be opposed by any pathologist. In my opinion, however, its bearing is not to be restricted to the processes just named; it must be made to embrace a much more extensive and therefore important domain, that of the true *tumours*.

We here enter a field which since the earliest times has

* Chassaignac, 'Gaz. des hôpitaux,' 1858, Mai 8; Busch, 'Langenbeck's A.,' vii, Heft 1, with references to the literature; Wittelshöfer, 'Langenbeck's A.,' xxiv, p. 57.

† Friedberg, 'Virch. A.,' xl, p. 353.

‡ Friedreich, ibid., xliii, p. 83; v. Buhl, 'Mittheilungen aus d. Münchener path. Inst.,' 1878, p. 300; Eastes, 'Med. Times and Gaz.,' Jul. 6, 1867. I saw an analogous case of hypertrophy of both hands and of the lower half of the face acquired late in life; the subject of it was a woman of about thirty, a patient in the clinic of Prof. W. A. Freund in Breslau.

been made the arena of multifarious speculations, and hence perhaps more than any other reflects the standpoint adopted by our science at various periods. To sketch even in its main features the development of the theory of tumours would indeed far exceed the limits of our lecture; and earlier theories, however noteworthy in themselves, have now essentially a mere historical interest. We need not now-a-days show that tumours are not parasites, *i. e. foreign* structures living at the expense of the human body, for the belief that they form *integral parts of the organism* has long since become interwoven with the fabric of our thought. It is then self-evident that the elements of a tumour will closely follow the *specific type* of the individual in whose body it arises—that, for example, in the tumours of man and mammals hairs and not feathers will be met with, and in the corresponding tumours of birds, always feathers. In other words, we hold it to be inconceivable that a tumour should ever contain cells or other elements unrepresented in the normal body of the individual the subject of it. Similarly it has ceased to be a matter of disputè that tumours, no less than other structures, are nourished by the blood, through the agency of vessels forming a part of the general circulation, and subject to its laws. On one point, however—the possible innervation of the vessels of tumours—we are very imperfectly informed; indeed, our knowledge of the general nerve-supply of tumours is very far from adequate. We know that when present they are directly connected with the centres, but whether they form a regular or merely a frequent constituent of tumours has not yet been made out. As to the presence and distribution of lymphatics in tumours there is also a dearth of trustworthy investigations. But all this cannot prejudice the really fundamental fact, without which a physiology of tumours would be impossible—that forming as they do integral parts of the organism, they are subject to general biological laws by which their growth, metabolism, and nutrition are controlled.

But just in proportion as this conviction has become established, has the difficulty of exhaustively defining what is to be understood by a tumour increased. True this difficulty has been enhanced by the classification as tumours of structures

which have no connection with them. I have not now in mind the *clinical* significance of the word *tumour,* which, as you know, is applied to every possible increase of volume recognisable by the sight or touch. In this sense the gravid uterus is a tumour; and the expression hepatic or splenic tumour is employed when these organs are more voluminous than normal, without any regard to the cause of the enlargement. But even from a purely anatomical standpoint, it will be well to sharply distinguish from the tumours a group of enlargements, which, it is true, often have a tumour-like aspect—all those, namely, which arise through the accumulation and *retention of liquid or cellular secretions,* &c. Such are accumulations of blood or *hæmatomas;* accumulations of transudation, as a rule inflammatory, or *hydroceles* and *hygromas;* then *follicular* and *mucous cysts, atheromata* and the different *secretion-cysts in the various glands;* in short all the formations usually embraced under the general name of *retention-tumour.* Their mode of origin, except in so far as this is deducible from the direct application of rules previously laid down, I have already briefly indicated (vol. ii, p. 711); the details of the process you will learn in connection with the special pathological anatomy of the individual organs; and if any of you are more than usually interested in this group I may refer you to the really exhaustive and final portrayal which it has received in Virchow's great work on tumours.* If this group be dismissed from the class of true tumours, there remain those which have for ages been regarded as the genuine *pseudo-* or *neo-plasms* or *growths,* and as such, justly contrasted with the former. We, however, for reasons which I have thoroughly explained, and which you will shortly be better able to appreciate, have determined on separating a highly important series of new formations, namely, the *infective tumours,* from the remaining growths; in this way once more effecting a considerable limitation of the entire domain. Let us now see whether it is possible to discover the guiding principle to this domain which, though curtailed, is still sufficiently rich and extensive.

To attempt a general description of a tumour would be a

* Virchow, 'Geschwülste,' i, pp. 128—286; Lücke, Pith.-Billr., Hdb. ii, p. 100.

foolish undertaking. For nothing more unlike than the various tumours in point of shape, size, colour, consistence, &c., could well be imagined. Microscopic examination, moreover, is calculated to increase the complexity of the appearances. Such examination reveals but one constant feature, *namely, that the tumours*—always employing the word in the limited sense given it by us—*invariably consist of actual tissue.* All the tissues, indeed, are represented in the various tumours; all the connective tissues, as well as all varieties of epithelium, muscle, and nerve. True they are not all equally common; much less are all of them present in every tumour. On the contrary, the textural structure of the growths is taken advantage of for purposes of classification. Thus Virchow divides them into three principal classes: (1) Tumours agreeing in composition with some one simple tissue of the body, *histioid;* (2) those built up of several tissues, the result being the production of a complicated structure with a definite typical arrangement of its parts, *organoid;* and (3) still more complicated forms, in which entire systems of the body are represented, though imperfectly, *teratoid* tumours. Yet if we include in the class "histioid" only such growths as consist solely of a single tissue, and neglect small epitheliomas and sarcomas, there remains, as Klebs* has very justly remarked, but a single form of histioid tumour, namely, the *angioma;* and even here there is not uncommonly a small amount of connective tissue between the blood- and vessel-sinuses: in all other tumours, blood-vessels at least are present in addition to the principal tissue. But if, on the other hand, one felt compelled to apply to the organoid tumours the notion familiar to us from normal biology, according to which an *organ* is an apparatus endowed with a special function, the term would then be utterly inappropriate; since even the most perfect adenoma is quite incapable of a regular physiological function. These difficulties at any rate are avoided by including Virchow's histioid and organoid tumours in one principal order, and simply subdividing this according to the tissue predominating in the growth. The tumours will then naturally fall into the following classes:—(1) Growths, the greater part of which is

* Klebs, 'Prag. Vierteljahrsschr.,' Bd. cxxvi.

formed on the *connective-tissue* type; embracing *fibromata, lipomata, myxomata, chondromata, osteomata, angiomata, lymphangiomata, lymphomata,* and *sarcomata;* as well as the mixed tumours resulting from combinations of the simple forms. These are for the most part conterminous with Waldeyer's* *desmoid* growths. (2) Tumours whose type is the *epithelia,* corresponding to Waldeyer's epithelial growths, namely, the *epitheliomata, onychomata, goitres, cystomata, adenomata* and *carcinomata.* (3) Those following the type of *muscular tissue, myoma lævicellulare* and *myoma striocellulare.* (4) Lastly, tumours of the type of *nerve-tissue,* the *neuromata,* and, according to Klebs'† recent communications, the *gliomata.* The second principal order would then be formed by Virchow's *teratomata*—tumours containing skin with hairs and sebaceous glands; sometimes bones, teeth, muscles; and even pieces of intestine with the characteristic glands; as well as cerebral matter. The commonest examples of the second order are the *dermoid cysts* of the orbit, genital organs, &c.

But the knowledge that a lipoma is a new formation consisting of adipose tissue, or that an osteoma is one consisting of osseous tissue, is of little avail for the definition of a tumour. For in obesity we have an increase of fatty tissue; every hyperostosis is a new formation of osseous tissue; and in compensatory hypertrophy of a kidney several tissues are produced and disposed in complicated order. The desire to distinguish the true tumours more especially from these hypertrophies makes it impossible for me to accept the definition given by Lücke,‡ although it has been most favorably received by his professional brethren. Lücke defines a tumour to be *an increase of volume due to a new formation of tissue in which no physiological terminus is arrived at.* But is a physiological terminus arrived at in hypertrophy of the heart or bladder, and where is the limit to the enlargement of a fever-spleen or a miasmatic goitre—where still more to that of a chronic inflammatory elephantiasis? To correctly define a tumour the chief stress must, I believe, be laid on one feature, namely, *the departure of the newly formed tissue from*

* Waldeyer, 'Volkmann'sche Vorträge,' No. 33.

† Klebs, 'Prag. Vierteljahrschr.,' Bd. cxxxii. ‡ Lücke, l. c., p. 4.

the morphologico-anatomical type of the locality. In hypertrophy of a uterus from imperfect involution or from chronic metritis, the typical form of the organ is always preserved; but a *fibro-myoma* is absolutely atypical. In hypertrophy of a stratified epithelium there is a mere increase in thickness, the regular stratification being fully maintained; while in *carcinoma* the arrangement of the newly formed epithelium is quite inconstant and irregular. In *adenoma* too, though the minute structure of the tumour bears a close resemblance to that of the gland involved, the disposition of the acini or tubes as a whole is very far from a repetition of that of the normal gland, such as is seen in true glandular hypertrophy. And while in the most extreme polysarcia the panniculus adiposus, though enormously developed, always adheres to the normal type and anatomical arrangement, nothing is known in normal human morphology of a form such as that presented by a *lipoma*. *Departure from the type* of the matrix is an important and indeed necessary criterion, not only of carcinoma, as claimed by Waldeyer,* but of *every true tumour*, no matter what its histological structure. But that this definition—*a new formation of tissue atypical in form*—is also inadequate, may be seen on turning for a moment to the history of inflammation. For what in the world could be more atypical than the recent bony callus thrown out after a fracture, than pleuritic or peritoneal adhesions, or than a mass of dense connective tissue in the myocardium—all of which are assuredly *new formations!* If then we hesitate to accept the conclusion which logically follows, and to remove every landmark and distinction between inflammation and tumour-formation, there must evidently be some additional factor whereby the growth or *tumour-like* neoplasm can be sharply and precisely distinguished from the inflammatory; and this can only be its *etiology*.

There is no chapter in our science so deeply involved in obscurity as is the *etiology of tumours*. Hypotheses, indeed, abound, and on consulting the text-books you will find an ample list of causes of tumour-formation. But of what value are they? We may fairly pass over some of the factors usually given, such as age, sex, social position, &c., since a

* Waldeyer, l. c.

direct causal relationship between these and the new formation cannot by any possibility exist; and, indeed, they are for this reason usually spoken of simply as "predisposing" causes. Among the supposed *direct* causes of tumours none, however, play a more important *rôle* than the so-called *local irritants of a mechanical or chemical nature, the local traumata.* The tendency to connect a malady originating locally with a local cause, is too firmly rooted in the human understanding not to have led to many attempts at explaining the development of tumours as dependent on previous wounds or the like. And, indeed, no inconsiderable number of cases has been placed on record in which the locality becoming the seat of a tumour had previously sustained some kind of trauma. But how little support the assumption of such a connection receives, even from statistics, you may learn from F. Boll. In a paper* already briefly alluded to, he comes to the conclusion that, because out of 344 cases of carcinoma operated upon in v. Langenbeck's clinic, in 42—say 12 per cent.—an antecedent trauma was reported to have occurred,* therefore recent statistics prove the etiological relation of injury to carcinoma! What is here apparent of carcinoma applies equally to all the neoplasms. An examination of the cases of tumour, 574 in number, occurring in the Berlin clinic during the last ten years gave almost the same percentage (14·3) of antecedent traumata.‡ Or, in other words, *investigation directed expressly to this point failed in almost 86 per cent. of cases to establish the previous occurrence of any kind of trauma.* Yet even if the conclusions to be drawn from the statistics of tumours were of an opposite character, it is clear that they could not carry any measure of conviction

* F. Boll, 'D. Princip. d. Wachsthums,' Berlin, 1876, p. 69.

† S. Wolff, 'Z. Entstehung von Geschwülsten nach traumatischen Einwirkungen,' I.-D., Berlin, 1874. A still lower percentage (7·06 per cent.) was obtained by A. v. Winiwarter ('Beiträge zur Statistik d. Carcinome,' Stuttgart, 1878, p. 48) from statistics directed to the antecedent occurrence of traumata in cases of carcinoma of the mamma in Billroth's clinic; Maas ('Berl. klin. Wochenschr.,' 1880, No. 47) reports even that out of 278 cases of tumour observed during three and a half years in his clinic, in four only was a trauma given as cause, *i. e.* in 1·44 per cent.

‡ Dooremal, 'Arch. f. Ophthalm.,' xix, Heft 3; Goldzieher, 'A. f. exp. Path.,' ii, p. 307; Schweninger, 'Zeitschr. f. Biol.,' xi, p. 341.

with them till placed side by side with statistics of wounds going to show that these had been followed by the development of tumours in a considerable percentage of cases. But how extremely frequent are contusions and other injuries of the shin-bone, and how very rare, fortunately, the osteochondromas and sarcomas of this part! How fearfully common would mammary tumours be if it were true that traumata led easily to tumour-formation, and how greatly must mammary tumours starting in the nipple preponderate over others; yet experience teaches that primary tumours of the nipple are very rare as compared with those originating in some of the deeper parts of the gland! But we may venture to dispense with statistics, which would at best prove a *post*, not a *propter hoc*, for we know of cogent reasons for rejecting the notion of a causal connection between injury and true tumours. We are very accurately acquainted with what follows a trauma: under favorable conditions *congestion*, under less favorable ones *inflammation*. Further, it is not long since we discussed the significance for tissue growth of repeated or of lasting arterial congestion as well as of inflammation; the former leads in certain circumstances to hypertrophy, the latter to an inflammatory new formation of tissue. That various epithelial and connective-tissue neoplasms taking the *form* of tumours are due solely to congestive and inflammatory disturbances of the circulation is the less likely to be denied by us, as I myself illustrated by corns, condylomata acuminata, elephantiasis, mucous polypi, hyperostoses, &c., the influences which congestive and inflammatory hyperæmias exert on the growth of the tissues. But he who would further infer therefrom that an inflammation which usually leads simply to the formation of connective tissue may suddenly, on some occasion, result in the production of muscle-fibres, glandular or cystic tissue, or even cerebral substance, to my mind deprives himself at starting of every chance of understanding the inner relationships of pathological processes. Of what utility would be the study of the laws regulating the formation of vessels and connective tissue in inflammation if such variations were possible? Or, rather, what kind of laws would they be to admit of such fundamental exceptions? In support of the statement that any kind

of cells increase or commence to proliferate as the direct result of an external traumatic impulse, there exists no shadow of proof, so far at least as the normal human organism is concerned. Whoever, then, upholds the doctrine that a tumour is the product of a proliferation, excited by a trauma, of any variety of cells, is logically compelled to assume that the organisation of the affected individual is abnormal, or, in other words, that the cells in his case react differently to those of the enormous majority of persons. The untruth of this assumption is, to my mind, demonstrated by the fact that a patient suffering from a tumour of supposed traumatic origin behaves in the usual way towards all other noxæ, and indeed reacts to traumata involving parts outside the region of the tumour with the inflammatory or other changes familiar to us as the typical consequences of injury. Hence the hypothesis must be narrowed so as to apply only to the locality in which the tumour develops; the assumption being that the tissues of this locality react abnormally to external noxæ. The extent to which such an assumption is justifiable will very shortly be discussed; and, at any rate, you cannot fail to perceive that when the theory is so formulated the real importance of the trauma as a *cause of tumours* is lost.

Nor is any greater importance to be attached to a second theory, which has met with the approval of a great many writers, namely, the *infective* origin of tumours—leaving out of account, of course, the tumours called by us infective. Despite the most strenuous efforts, no evidence for the epidemic or endemic occurrence of true tumours has as yet been forthcoming. Moreover, there is not a single accredited case of the communication of a tumour from one individual to another. No surgeon has ever become infected by a tumour during the operation for its removal, nor has a husband ever acquired an epithelioma of the penis from the uterine cancer of his wife. How numerous have been the fruitless attempts at inoculating animals with tumours removed from man, and even from other individuals of the same species! When a piece of periosteum is inserted under the skin of a dog or of a rabbit, it is transformed into a plate of bone; and a small quantity of living epithelium when introduced into the anterior chamber of the eye may

form the starting-point of a really considerable epithelial growth. Hence it is no way remarkable that living epithelium from a carcinoma should, when implanted in the subcutaneous cellular tissue, go on proliferating for a time. But this falls far short of constituting an inoculation such as we have witnessed in tuberculosis, for instance; for in this disease inoculation gives rise to new formations making an integral part of the organism, undergoing marked subsequent development, and essentially affecting the condition of the animal inoculated. None of these results attends the inoculation of true tumours; the introduction of pieces of the most juicy and cellular medullary cancer either into the blood or under the skin is at best attended by a proliferation of moderate intensity, followed after at most a couple of weeks by the disappearance of the fragments through resorption, the animals having sustained no inconvenience except that resulting from the wound.* Still less success has attended the inoculation of myxomata, chondromata, myomata, &c.; there is not the least attempt at subsequent development. Even when the material is transferred with the greatest possible precautions, either from dog to dog, cat to cat, or horse to horse, the constant result is resorption with or without suppurative inflammation, and ultimately simple cicatrisation. All things considered, I can only state my conviction that even for the carcinomata, to say nothing of the other true tumours, no author—even when like W. Müller† he speaks with such a strong sense of conviction—has ever brought forward the shadow of a proof that a "virus" comparable to that of syphilis, glanders, and other infective diseases, participates in their production. But if it be asserted that the specific virulence of the malignant tumours is to be deduced not so much from their communicability to a second individual as from their behaviour in the organism of their host, I reply that this virulence, as you will shortly hear, has its own peculiar conditions.

* Langenbeck, 'Schmidt's Jahrb.,' xxv, p. 99; O. Weber, 'Chirurg. Erfahrungen u. Untersuchungen,' p. 259, Berlin, 1869; Billroth, 'Wien. med. Wochenschr.,' 1867, No. 72; Lebert und Wyss, 'Virch. A.,' xl, p. 532; Doutrelepont, ibid., xlv, p. 501; Virchow, 'Geschwülste,' i, p. 87; 'Arch.,' lxxix, p. 188.

† W. Müller, 'Jen. Zeitschr. f. Med. u. Naturw.,' vi, p. 456.

But what shall I say then of the influence on the origin of tumours of *alimentary noxæ,* and more especially of *emotion* and *nervous excitement*—factors which, chiefly in the older literature, are accredited with playing a part? However violent and intense the action of these noxæ and excitations, I know of no way in which they could influence the growth of a part except by disturbing the circulation; but if you agree with me in this, there is an end to the possibility that true tumours can ever be conditioned by such factors. Only *one* resource appears to be left, namely, the *congenital disposition* of the embryo. As regards the true *teratomata* such a view has already been announced by other pathologists. Lücke* in particular has produced very strong evidence that the *dermoid tumours* are invariably congenital structures, which depend ultimately on abnormal invaginations or constrictions of the epiblast during the formation of the orbital and buccal cavities, of the neck, and also of the testicles, ovaries, &c. But I cannot conceive why the same view should not be true for all the remaining growths, viz. Virchow's histioid and organoid tumours.

True, if you ask me wherein the abnormality in the disposition of the embryo that becomes the starting-point and cause of a tumour consists, I can only answer with hypotheses. The simplest view appears to me undoubtedly to be that in an early stage of embryonic development more cells are produced than are required for building up the part concerned, so that there remains unappropriated a quantity of cells—it may be very few in number—which, *owing to their embryonic character,* are endowed with a marked capacity for proliferation. Anyone who more closely considers this hypothesis will, I believe, be led involuntarily to refer the production of superfluous cells to a very early stage, possibly to the developmental period between the full differentiation of the layers of the blastoderm, and the complete formation of the rudiments of the individual organs. So at least we shall, I think, most easily understand why this abnormality gives rise later on, not to general hypertrophy of a part, but simply to a histioid tumour, *i. e.* to excessive growth of one of the tissues of the part. Moreover, it is possible that the super-

* Lücke, l. c., p. 126.

fluous cellular material may be more or less equally distributed over one of the histogenetic germinal rudiments or remain confined to one spot. In the latter case the *local rudiment* of an organ, or only a definite region of the same, would subsequently become involved in the tumour-formation; in the former, on the contrary, the rudiment of an entire system, *e. g.* of the skeleton or of the skin, would take part in it. You will not however attach more importance to this view than can be fairly claimed for it; it is only a modest attempt at formulating somewhat more intelligibly the hypothesis of an embryonic disposition. Owing to our imperfect knowledge of the details of the process of growth, we are unfortunately still compelled to have recourse to guesses; and I put no value on the formulation itself, but am ready at any moment to exchange it for a better. The only point on which I lay stress is that *the real cause of the subsequent tumour is to be sought in a fault or irregularity of the embryonic rudiment.*

That portions of embryonic tissue, if present in the body of a fully grown animal will behave peculiarly, is no longer a mere hypothesis, but a fact certainly established by means of experiment. In the first instance Zahn,* and then Leopold,† carried out such experiments, and obtained strictly harmonious results. The latter, working in this institute, systematically investigated the fate of different tissues, portions of which were introduced into the anterior chamber, or into the abdominal cavity, of living rabbits; and it turned out that pieces of tissue taken from rabbits already born, irrespective of the animals' age, became completely resorbed or greatly shrunken, or in rare cases retained their original dimensions; while pieces taken *from a fœtus still unborn* not only lived on in the new foreign organism, but almost always *grew there in a very surprising way.* Thus Zahn and Leopold were able to follow the growth of pieces of fœtal cartilage—a tissue preferred by them on account of its characteristic appearance—till they had increased enormously, even to two or three hundred times their original size, and in this way

* Zahn, "Sur le sort des tissus implantés dans l'organisme." In the protocols of the 'Congrès méd. internat. de Genève,' 1878. This short report has not, so far as I know, been followed by a more detailed one.

† Leopold, 'Virch. A.,' lxxxv, p. 283.

produced a mass having all the properties of a true tumour, an *enchondroma.* This tumour as a rule continued to increase for several months till the animal's death, and never at any rate sustained any diminution; much less was it resorbed.

While, accordingly, the validity of our hypothesis is not open to doubt, you will still wish for better evidence of its actual authority than is afforded by the *per exclusionem* line of proof hitherto adopted by us. Convincing *positive* evidence cannot in the nature of the case be produced; yet there is a whole series of facts highly favorable to the view just expounded. Of these I may give the first place to the *hereditary* transmission of tumours.* In the literature of the subject is recorded a large number of observations on the appearance of the same kind of tumour in the several successive generations of a family. This fact is particularly well established for carcinomas, enchondromas, osteomas, fibromas, lipomas, adenomas, angiomas, neuromas; and the inheritance has just as often been observed to occur through the paternal as through the maternal side. It is moreover of interest that the inheritance of tumours sometimes forms an exact parallel to that of supernumerary fingers appearing on the same extremity; *i. e.* it is, for example, the mamma that generation after generation becomes the seat of the adenoma or cancer. In other instances the tumour formation is transmitted, not in a definite locality, but in a *system;* in this way different members of a family may for several generations be afflicted with enchondromata, appearing in one on the pelvis, in a second on the humerus, in a third on the femur, and so on. Between enchondromata and osteomata —which of course bear the same relationship to one another as do cartilage and bone—there is besides a mutual inheritance. That those cases, moreover, where the mother has an adenoma of the breast and the daughter a cancer of this organ may be explained by heredity, will be clear from what you will shortly learn of the nature of the cancerous process. Lastly, that the occurrence of the same kind of tumour in children of the same parents† may point to hereditary influ-

* Lücke, l. c., p. 55.

† Cf. Genersich, 'Virch. A.,' xlix, p. 15 (also contains older references from Schiffner); Rump, 'Virch. A.,' lxxx, p. 177, multiple neuromas in two brothers. Not long since were observed here in Leipzig two cases of

ence, although such has not perhaps existed in the immediate progenitors, need not at present be dwelt upon more minutely.

Further, our view is thoroughly supported by the *congenital appearance* of tumours, whether inherited or not. That the teratomata proper are often born with the child is well known; but of other tumours it is not usual to reckon as commonly congenital any but small *pigmented moles* and angiomas. No sooner, however, is the attention more particularly directed to this factor, in everyday experience, at the *post-mortem* table, and in the literature of tumours, than we become speedily convinced that congenital growths of all kinds are by no means so uncommon as is supposed.* Small fibromas and lipomas† of the skin and subcutaneous fat are far from rare in the new-born; and I may remind you of the congenital enchondromas of the skull, the spinal column, and even the fingers;‡ of the myoma of the maxillary region,§ the adenoma of the kidney,|| the rhabdomyoma of the heart,¶ and the goitrous nodules of the thyroid gland, repeatedly observed in the new-born.** A few cases of sarcoma†† and even of congenital cancer have also been described.‡‡ But a very considerable extension of the domain of congenital tumours is effected by embracing in it those cases also which have been attended by a fatal issue during the earliest years of life. For a number of examples of carcinoma should then be included in the category—examples too in which marked metastases occurred (in lungs and pleura,§§ adrenals, lungs and

primary *sarcoma of the kidney* with metastases in lung and liver in two brothers, both of whom died when three years old.

* Cf. among more recent statements Maas, 'Berl. klin. Woch.,' 1880, No. 47, and especially Ahlfeld, 'A. f. Gynäk.,' xvi, Heft 1.

† Cf. C. Vogt, 'Einige congenitale Lipome,' I.-D. Berlin, 1876.

‡ Virchow, l. c., i, p. 477.

§ Schuh, 'Pathologie u. Therapie d. Pseudoplasmen,' 1854, p. 252. A large congenital myxofibroma of the galea tend. is described by Chiari, 'Jahrb d. Kinderheilkunde,' xiv, p. 230.

|| Weigert, 'Virch. A.,' lxvii, p. 492.

¶ Virchow, l. c., iii, p. 98.

** Virchow, ibid., p. 54.

†† Vide Ahlfeld, l. c. Further, Charbon et Ledegauck, 'Bull. de l'acad. royale de méd. de Belgique,' xx, Heft 5 (Sarcoma of the right side of the face); Dawson, 'Amer. Journ. of Obst.,' 1879, Jan., p. 160 (Myxosarcoma of the right thigh).

‡‡ Cf. Ahlfeld, l. c.

§§ Aldewie, 'Lancet,' Oct. 21st, 1876.

liver,* kidneys†); also some of the highly pernicious retinal gliomas,‡ as well as of the myomas and myosarcomas of the kidney.§

True, the congenital tumours form but an insignificant minority of all growths; and it would be a bad look-out for our theory were we obliged to depend on them alone for support. We do not, however, claim that the tumour itself is congenital, but merely that its *rudiment* is; viz. we assume, in accordance with the view formulated by us, the existence of an excess of cells as compared with the physiological standard, out of which excess a tumour may ultimately develop. Thus an extremely small and scarcely perceptible nodule of the skin or subcutaneous fat, or of a gland, may later on give rise to a bulky fibroma, lipoma, or adenoma; an insignificant pigmented mole may become the starting-point of a large melanotic growth, and a small cutaneous cyst that completely escapes notice develop into a dermoid of large size. Still more: it is quite conceivable that the cell-clusters representing the rudiment of the tumour may be absolutely indistinguishable from the physiological elements of a part by any means at present at our disposal. To distinguish them is not difficult when such abnormal cells-groups are present in a dissimilar tissue, as for example where islands of cartilage persist in the midst of fully formed bone, of which Virchow|| has lately communicated a couple of very instructive examples. But how will you determine from the appearances of a group of epithelial cells, of cells of the lymphatic glands or of the bone-marrow, whether or not they are embryonic survivals?

This is indeed by far the most common antecedent to the development of a tumour. The new-born infant brings with

* Unpublished observations of my own.

† Rohrer, 'D. primäre Nierencarcinom.,' I.-D., Zürich, with copious references.

‡ Cf. Leber, 'Graefe-Saemisch Hndb. d. Augenheilk..' v, p. 714, with very full references.

§ Eberth, 'Virch. A.,' lv, p. 518; Cohnheim, ibid., lxv, p. 64. I subsequently saw a quite analogous case, Prep. 18 in the Museum at Breslau, year 1877, described by Landsberger, 'Berl. klin. Woch.,' 1877, No. 34; further, Huber u. Boström, 'D. A. f. klin. Med.,' xxiii, p. 205; Marchand, 'Virch. A.,' lxxiii, p. 289.

|| Virchow, 'Berl. akad. Monatsb. Phys.-math. Kl.,' 6/12, 1875.

it into the world, not the tumour, but merely the superabundant cell-material, and from the latter, if circumstances be favorable, a tumour may grow later on. I wish once more, however, to warn you against adhering too closely to the expression, "suberabundant cell-material;" it would perhaps be more correct to speak of a material having an inherent potentiality for subsequent tumour development. For the development of the tumour *depends* on this power, which for the rest is simply the quality so very commonly manifested in individual instances of inheritance and development. When in the son of a long-nosed father, the nose remains till the eighth or tenth year, or even later, quite proportional and in no way remarkable, and then grows disproportionately longer and larger, no one doubts that the potentiality for growth existed in the nose from the first, although the most careful and accurate microscopic examination of this same nose in the earliest years would fail to discover it. Essentially the same notion is to be understood by potential disposition to tumour formation; and should you prefer, instead of the expression adopted by me, to speak with Ziegler* of a group of cells which from the first "*have received an abnormally strong vital impulse,*" I can see no objection to it. The capacity for abundant cell-production is, by virtue of its constitution, inherent in that material; and in order that this production, and with it the tumour formation, may follow, no nervous impulse or other excitation is required, but only and solely *an adequate blood-supply.* The rôle played by the latter in the origin and growth of tumours is nowhere more clearly taught than by the development, or rather rapid growth, of certain neoplasms, when the blood-supply of the locality in which they are situated is increased for physiological ends. The exostoses "originate," as a rule, at the time when the growth of the skeleton is most active, viz. at the period during which blood-vessels are most abundantly formed in it. The dermoid tumours increase chiefly at puberty, when the appearance of the beard, &c., points to the occurrence of active developmental processes in the epiblast.† The cystomas of the ovary do not commence growing till puberty; and how greatly the

* Ziegler, 'Lehrb. d. path. Anatomie,' i, p. 101.

† Lücke, l. c., p. 127.

growth of tumours of the breast or ovary becomes accelerated at every pregnancy is universally recognised. From this standpoint it is quite conceivable that oft-repeated arterial congestion, or even inflammatory hyperæmias, may stimulate the rudiment of a tumour to develop; that, in other words, the theory of the traumatic etiology of tumours may have a certain degree of applicability, though in this essentially modified form. Maas* saw, in a man of twenty-three, the sudden and rapid growth of a small, pale red angioma, situated above the inner angle of the left eyebrow, after the skin of the forehead, including the angioma, had been divided transversely above the superciliary ridge by a sword-cut. The angioma had remained unaltered from birth, but now, within a year, it grew into a large, hemispherical, bluish, vascular tumour, while the remaining easily healed sword-wound left behind it a mere fine linear cicatrix. A similar sequence of events may have occurred in some of the sarcomas of the choroid excited by traumatic influences, as well as in many other tumours, though in these cases we are not in the happy position of being able to detect the rudiment of the tumour prior to the infliction of the trauma. It is also possible that the constant wearing of heavy earrings by an individual predisposed to cutaneous fibromas may lead to the appearance of true fibromas in the lobe of the ear,† and that, where an entire system, or an isolated part of the body, has a congenital tendency to tumour production, a trauma may sometimes determine the particular spot in which the growth will take place. These are, we say, possibilities; but I cannot attribute much interest to them while statistics give the traumata the subservient place they at present occupy even among the agencies inducing tumours. When I reported that in 86 per cent. of all tumours no history of an antecedent trauma was discoverable—and if the notion of a tumour be restricted as we have restricted it, this percentage will be considerably increased—this proves at least that the development of a tumour may occur independently of a trauma. As regards slowly growing tumours—and these form the

* Maas, 'Berl. klin. Woch.,' 1880, No. 47.

† Saint-Vel, 'Gaz. des hôpitaux,' 1864, 84; Knapp, 'A. f. Augen. u. Ohrenheilk,' v, 1876.

enormous majority—there is no doubt whatever that the ordinary circulation is sufficient to set up development in the rudiment. But the impulse that excites and liberates this development must as a rule evade detection, if for no other reason, because we are ignorant of the causes which have checked and impeded the development of the superabundant germinal material. How many individuals with bodies containing rudiments of tumours may die without the slightest growth having taken place in them! Is it, perhaps, the resistance of the normal tissues that hinders the development of the abnormal germinal material? This is an idea obviously suggesting itself, and hence it may fairly be asked whether a trauma may not also exert an influence on the growth of a neoplasm by enfeebling the physiological resistances in the neighbourhood of the rudiment. But to this question we shall return when we come to deal with the malignant tumours.

The factors already dwelt on may suffice for the establishment of our hypothesis; its actual value, however, can only be appreciated when the test of experience is applied to it. In other words, we must inquire *whether the peculiarities of tumours are in some degreee explainable by its aid.* Now I think that even a greater measure of success will attend the employment of our hypothesis than that of any other. For on our view it becomes intelligible in the first place, that a tumour may be composed of *any of the tissues,* not only of those which, like the epithelia and connective tissues, constantly produce new elements during the whole of life, but of those too which, like muscle and gland substance, do not normally appose material except under the influence of definite excitations; and thirdly, of those which after a certain age cease to give birth to new elements, such as the central nervous system. Independently of any congestive or inflammatory hyperæmia, a growth, depending on the presence of suberabundant embryonic material, takes place, giving rise in the subcutaneous fat to a lipoma, in bone to an exostosis, and in the absence of all miasmatic influence, to a goitrous nodule. Similarly, without any motor or secretory stimulation, a myoma or an adenoma is developed from the abnormal cell-group; while in the brain, a congenital rudiment gives rise to a new formation at a period when the

cause is found in a circumstance to which I called attention in my introductory remarks on tumours. The uterus of man and mammals may be said to possess an inherent capacity for growing under certain conditions long after the termination of the growing period proper, but this is only another way of saying that germinal material is present in every uterus, and only awaits a physiological stimulus to actually grow. If this be so, the probability is great that this germinal material will sometimes develop in the absence of physiological stimulation, and then of course irregularly, atypically. Moreover, it is quite possible that the tendency to do so will be more marked when the physiological stimulus, *i. e.* conception, has never or only seldom occurred, and the germinal material has failed to undergo further normal development. How excellently this assumption agrees with the facts that the uterine myomas never develop till after puberty, and have a special predilection for old maids, is sufficiently obvious. And that this is actually the case I must still maintain, as will the pathological anatomist with me, despite the denial of some practical gynæcologists. The latter base their conclusion on those myomas essentially which, owing to their size, give rise to bleeding or other morbid phenomena, while we take into account in addition the decidedly larger number of those usually small fibro-myomas which have never been subjected to medical treatment, and are, so to say, accidentally discovered post mortem.

But what about the myomas, or rather *adenomyomas of the prostate*, those new formations, that is, which are commonly termed *hypertrophies of the prostate?* These are neither inflammatory neoplasms nor—in spite of their usual designation—legitimate hypertrophies; they are undoubtedly true *tumours*, partly glandular, but in greater part muscular in structure. And yet the existence of a *physiological* disposition to exceptional growth in this organ is absolutely out of the question, while unprejudiced observers are unanimous in believing that traumatic irritation has no share in the production of hypertrophies of the prostate. This is indisputably true; nevertheless the key to the explanation of prostatic myomas is, in my opinion, supplied by *embryology*. The prostate develops, you are aware, at the point of entrance

of Müller's ducts into the sinus urogenitalis; we have therefore here again to deal with a locality where the embryological processes are complicated in a high degree. I may remind you of the common variation in size and shape of the sinus prostaticus, of the many irregularities in the formation of the glandular part of the prostate, of the production of folds in the neighbourhood of the colliculus seminalis, of the varying arrangement of the ductus ejaculatorius and the canaliculi prostatici. With such conditions, what could be more natural than that superfluous embryonic muscular or glandular cell-groups should occasionally remain over during the development of the prostate, and form the material out of which myomas and adenomas may subsequently arise?

On the other hand, the frequent occurrence of tumours of the *testicles,* when these organs are *retained in the abdomen,* may perhaps be explained—after the analogy of the unimpregnated uterus—on the supposition that, owing to the retention, the germinal material present does not arrive at regular development. Moreover, the adenoma of the mamma, so remarkably frequent in unmarried or sterile women, to which Velpeau* long ago directed attention, is clearly to be regarded as a companion picture to the myoma of the uterus.

Our hypothesis receives its strongest confirmation, however, on applying it to the so-called *heterologous* growths—those, that is, which in structure depart completely from that of the substratum in which they originate. Only when you consider to what conclusions one is here inevitably driven unless our hypothesis be adopted, can you fully estimate how completely justified it is. Or ought you, in opposition to every law of physiological development, to believe that cartilage may be suddenly developed from glandular tissue, that connective tissue may give rise to epidermal or glandular epithelium, that the kidney can produce striped muscle-fibres, that from pulmonary tissue bone may originate, and that all this may happen in the absence of any recognisable determining cause? Moreover, the strangeness is enhanced a thousandfold by the fact that *the heterologous tumours display a strict regularity as regards the localities affected by them.*

* Velpeau, 'Traité des maladies du sein,' Paris, 1854, p. 351.

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* Velpeau, 'Traité des maladies du sein,' Paris, 1854, p. 351.

The *enchondromata of bone* never arise from the parts remaining cartilaginous, *i. e.* from the articular cartilages, but invariably proceed from the midst of the fully formed bone itself, while enchondromata of the soft parts have such a preference for the parotid gland and the testicles that their occurrence elsewhere may be disregarded. The *subcutaneous dermoids* are very rarely seen except in the regions of the orbit, mouth, and neck, as well as in the anterior mediastinum, while of the *deeply situated dermoids* the vast majority occur in the ovaries and the testicles, though they have in a few instances been met with in the brain and in the female pelvis close to the ovaries. *Heterologous rhabdomyomata* are confined to the urogenital system; at least they have never hitherto been observed in any of the other organs. Is the occurrence of these tumours in certain localities the result of accident merely? And does the connective tissue of these parts possess the power of producing cartilage or cutaneous epithelium, or striped muscle-fibre, though all other connective tissues, while histogenetically identical with the foregoing, possess no such power? And now contrast with this the view that a slight abnormality had occurred in the formation of the first rudiments of the organs, causing a group of cells to be unappropriated or to be transferred into an unnatural situation! The enchondromata of bone originate from the midst of the fully formed tissue because they are derived from *vestiges of embryonic cartilage* which had not been used up in constructing the bone but remained surrounded by osseous matter. The rudiments of the enchondromas of the parotid region consist of unappropriated particles derived from the cartilaginous parts of the *branchial arches*; and that the favourite seat of the superficial dermoids is the face and neck may be explained in the simplest possible way by assuming, with Lücke, that the folding in of the skin to form these parts occurs abnormally. Moreover, on recalling how complicated are the events to which the *urogenital system* owes its origin, and remembering more especially in what intimate relationship the first rudiments of this system, the Wolffian bodies, stand, on the one hand, to the corneous layer, and, on the other, to the primitive vertebræ, it is easy enough to see how it comes that the

principal organs of the urogenital system should be the seat of dermoids as well as of muscular, cartilaginous, and bony tumours. Only a slight error in the mutual abstrictions would be required in order to supply from the corneous layer the rudiment for the dermoid, and from the primitive vertebræ the rudiments for the myomas, enchondromas and osteomas. The pelvic dermoids occurring in the females of animals and man no doubt originate in the same way, and were probably at first *supraovarial,* while the *mediastinal* dermoids* rank with those of the neck. Those met with in the brain may also unhesitatingly be referred to the connection of the central nervous system with the epiblast in the embryo. The adenomata which have occasionally been observed in the axillæ of women are also to be placed in this category; for, as Lücke† rightly pointed out, they originate in small *accessory mammæ,* which though formed have remained rudimentary. The same applies to the enchondromata and osteomata of the lungs, whose development, I consider, is due solely to vestiges of embryonic cartilage which have missed being appropriated to the building up of the cartilaginous walls of the bronchi. But I have, I think, supplied you with illustrations sufficient to make the theory of embryonic rudiments plausible enough as applied to the heterologous tumours, the history of which becomes intelligible to the scientific understanding only on the basis of this hypothesis. It would, of course, be impossible to pass in review every observed case of heterologous tumour-formation; and it must be left to the future to explain each as it arises from the standpoint of embryology—on the general principle, that is, which has long been adopted for the malformations—as Thiersch‡ has already explained the cancroids originating outside epithelial organs, and Lücke and Klebs§ some other heterologous growths.

But our theory throws a flood of light on another side of the history of tumours, inasmuch as it *explains the peculi-*

* Virchow, his 'A.,' liii, p. 444.

† Lücke, l, c., p. 281.

‡ Thiersch, 'Der Epithelialkrebs, namentlich der Haut,' Leipzig, 1865.

§ Klebs, 'Virch. A.,' xli, p. 1; 'Handb. d. pathol. Anat.,' i, p. 802; cf. also Waldeyer, 'A. f. Gynäk.,' i, p. 252; Coblenz, 'Virch. A.,' lxxxiv, p. 26; Fischel, 'A. f. Gynäkologie,' xv, Heft 2.

arities of their conformation and histological structure in what I take to be a satisfactory manner. When defining a tumour, we attached great importance to the fact that it deviates from the morphological type of the locality; that it is, in a word, *atypical*. Even the most homologous and benign tumour, a lipoma or a fibroma, a smooth myoma or an angioma, a goitrous nodule or an exostosis, however closely it may repeat the structure of the substratum, yet departs from it in contour and conformation. A lipoma is a more or less sharply circumscribed tumour, lying in the adipose tissue or projecting far beyond it, and the same applies to the tuberous fibroma; uterine myomata may have no connection with the uterus, except by means of a narrow pedicle; a goitrous nodule is ordinarily sharply defined against the other tissues of the thyroid; and the exostoses often describe the most singular figures. If these tumours were really the result of a simple "local irritation" of the elements of the affected part, might it not reasonably be expected that, for example, an entire lobe of the thyroid gland should undergo a uniform enlargement, such as involves the whole organ in miasmatic bronchocele; that a hyperostosis should develop as it does in syphilis; that a thickening of the connective tissue should take place, resembling that in chronic inflammatory elephantiasis? Now, this apparently strange atypical character is at once comprehensible on the theory of embryonic rudiments. For the rudiment of the tumour, as postulated by us, arises it is true during embryonic development, but it consists of an abnormal and redundant cell-group; as is most clearly evidenced by the fact that the development of the affected part proceeds to its termination in a manner no less regular and perfect than does the body as a whole. This redundant material is not of course subject to the control of the plastic forces of the organism; so that should it at any time commence growing, the resulting tumour must necessarily be *atypical*. Histologically the tumour must correspond with the substratum in which it arises, when its rudiment consists of a group of superfluous cells embedded in tissue of the same kind. Such is the case, for example, when redundant embryonic fat-cells remain lying in the subcutaneous cellular tissue, embryonic muscle-cells in muscular tissue, or embry-

onic epithelium in an epithelial organ. There must then be a histological resemblance, but by no means a *morphological* one; for the conditions of growth, both as regards time and space, have meanwhile been altered. In the so-called heterologous tumours even a histological similarity is, of course, out of the question; since the rudiments of such tumours are, so to speak, "aberrant."

Yet the agreement between the homologous tumours and their substratum in *histological* characters has its limits; it is far from absolute. It is undoubtedly true that the cell-forms of epithelial tumours are usually such accurate representations of the type prevailing at their place of origin that this type may usually be recognised in the growths. Thus in cancer of the skin, mouth, pharynx, and œsophagus, as well as of the vagina and lower portion of the rectum, we regularly find prickle- and ridge-cells, together with characteristic squamous epithelium. In cancer of the upper part of the rectum, of the rest of the intestine, of the body and neck of the uterus, we find cylindrical epithelium. Again, when the stomach is the seat of the carcinoma, the cells agree in character either with the parietal or with the central cells of the gastric glands; while in cancers of the kidney and breast, the cells follow the type of the urinary tubules and mammary epithelium respectively. Not only so, but the subsequent fate of the tumour-elements is essentially determined by the nature of the processes which are wont, in a physiological condition, to take place in the cells of the localities in question. Enchondromata and periosteal tumours *ossify*; goitrous nodules undergo *colloid* metamorphosis; the cells of a cutaneous cancer cornify, those of a mammary cancer undergo fatty degeneration, just as happens in the cells of the normal gland during lactation. But even in the ordinary cancroid we often meet with strange cell-forms, though maintaining the squamous type; and more especially with a much larger number of bulbiform *concentric epithelial pearls* than is ever found in normal stratified epithelium. In many carcinomas there is no lack of epithelial cells of less pronounced or more indefinite type. Take further the *cystic tumours of the ovaries*; the characteristic epithelial elements here perfectly correspond with the cells of Pflüger's epithe-

lial tubes, in the unappropriated vestiges of which we see, with Klebs,* the starting-point of the new formation; but the conformation, as well as the internal disposition of the parts of the larger cystomata, offers such a contrast to the physiological product of the development of Pflüger's tubes, the ovarian follicles, that these cystic tumours long passed for completely heterologous growths. Nor is this departure from type restricted to the epithelial tumours alone. In a true *lymphoma*, however perfect the resemblance between its cells and ordinary lymph-corpuscles, you will generally seek in vain for the regular arrangement of reticulating cords of medullary substance, for the follicles, and for their relation to the lymph-sinuses; all of which are preserved in hypertrophy, whether due to inflammation, leukæmia, or typhoid. A *cavernous angioma* departs enormously, not only in form but in general aspect, from ordinary blood-vessels, and in microscopic stucture its trabeculæ show but a faint resemblance to vessel walls. The most interesting and certainly fundamentally important point, however, is the close agreement between entire categories of tumours and *embryonic forms of tissues*.

This is already apparent in the *amyelinic neuromata*, of which Virchow† holds the characteristic composition to be extremely fine nerve-fibres, abundantly furnished with long oval nuclei. Very marked embryonic characters are found, moreover, in the *muscle-fibres of the rhabdomyomata*. The elements of these tumours have been described by every observer as consisting of extremely fine fibres without any recognisable sarcolemma, or of spindle-cells marked by a transverse striping. Among the *chondromata*, too, we often enough find forms which, owing to their wealth of cells and to the absence of the cell-capsules, vividly remind one of embryonic cartilage. But most striking of all is the embryonic character of the tissues in two highly remarkable and sharply defined varieties of tumour, for which there is actually no prototype in the normal adult organism, namely, *myxoma* and *sarcoma*. A *myxoma* consists, as you know, of a gelatinous, transparent, mucin-containing mass, in which a larger or

* Klebs, 'Virch. A.,' xli, p. 1; 'Handb. d. pathol. Anat.,' i, p. 802.

† Virchow, his 'A.,' xiii, p. 256; 'Geschwülste,' iii, p. 282.

smaller number of cells, some round, some spindle, and some branched, are embedded. No such tissue is found, we have said, in the normal adult organism; there is at most a mere indication of it in the vitreous humour. In the embryo, on the other hand, it is extensively developed, and regularly constitutes the first stage in the formation of collagenous and fatty tissues. When a large subcutaneous myxoma is met with in the thigh of an adult, for instance, is one really to believe that the subcutaneous cellular and adipose tissues have reverted, not simply to juvenile, but to *intra-uterine* habits, and have transformed the albuminous material conveyed them by the blood-stream, not, as is usual, into collagen and fat, but into mucin? As compared with this assumption, ours seems to me to be admirably simple. For supposing the rudiment of the tumour to have arisen in a corresponding period of embryonic life, it will be precisely the physiological function of its cells to produce *mucous tissue,* so that the subcutaneous myxoma is robbed of its foreign character, and becomes one of the most homologous of all the varieties of tumours.

Strictly analogous conditions prevail in *sarcoma*—that remarkable form of tumour which long remained a riddle to the pathologist and surgeon, till Virchow* found the key to its interpretation, and announced that the sarcomata are *connective-tissue tumours, in the formation of which the cellular elements preponderate.* Nothing could in fact be more appropriate than this definition, which at the same time renders simply intelligible the compound tumours of such common occurrence—the fibro-, chondro-, osteo-, and melano-sarcomas. When, says Virchow, the cells of a fibroma, chondroma, &c., get so greatly the upper hand that the intercellular substance becomes completely thrown into the shade, we have before us a sarcoma. This is a very excellent, if I may so say, *logical* formulation—nevertheless it is no *explanation.* It is clearly necessary that an explanation should elucidate the causal conditions on which the preponderance of the cells in the tumour depends. In the adult organism we are, it is true, acquainted in inflammation with an inundation of the connective tissue by cells, yet this point of resemblance

* Virchow, ibid., ii, p. 177.

can be of no service in explaining the sarcomata, since the processes are totally different in the two cases. In physiological growth, which forms our safest guide, the changes taking place during development are the very opposite of those occurring in inflammation; *the cells of the connective tissue move asunder, and the intercellular substance increases as compared with the cells.* If we desire to find the histological prototype of a spindle- or of a round-cell sarcoma we must indeed go far back to the earliest embryonic period; only in the first beginnings of development of the connective-tissue organs is there a stage when these organs are composed of tightly packed cells, together with a very small amount of ground substance. And now, I ask you, can you really credit the cells of the dura mater, of the choroid, of a fascia, or of the areolar tissue in the adult with the capacity which, according to the moulting- and rejuvenescence-theory of Schultz-Schultzenstein and Stricker, they possess, of suddenly producing tissue-masses, having embryonic, and markedly embryonic, characters? Or may you not still prefer the theory of superfluous, and hence unappropriated, embryonic cell-groups originating at an extremely early period? If a little cluster of closely aggregated cells remains unappropriated, and becomes arrested, wholly or partly, in this early stage, is it not quite conceivable—nay, necessary—that the tumour subsequently developed from it should consist completely or partially of enlarged, it may be, but yet closely packed spindle-cells—that it should form a pure *spindle-cell sarcoma,* or one containing fibromatous tissue, viz. a *fibro-sarcoma.*

I may leave you to apply what has been said to the still more complicated mixed tumours, which so often make havoc of the customary classification. You have now been made acquainted with the guiding principle, and to do more than this is not the office of these lectures, at least as I conceive it. My main object—namely, to prove to you that the embryonic theory is capable of explaining all the peculiarities of tumours—has, unless I am utterly deceived, been satisfactorily accomplished. Having first of all rejected all other supposed causes of tumours, more especially traumata and infection, we found in the congenital appearance and in the inheritance of numerous growths a positive basis for our

assumption, and we were able with its aid to explain, not only the usual situations of tumours, but their constitution also, and this with equal success for the homologous and the apparently heterologous tumours. Then, having by objective analysis of the neoplasms, discovered that macroscopic and microscopic *atypia* is one of their constant characters, our hypothesis secured us the satisfaction of seeing why tumours must necessarily be atypical. Relying on these factors, we may now, I think, venture to define a tumour as *an atypical new formation starting in an embryonic rudiment.* Herewith the tumours are brought into direct relation to the so-called malformations—a probability pointed out to you at the first. They therefore constitute in some sense a subdivision of the *monstra per excessum,* the other forms of which, unlike tumours, are, it is true, present at birth, while only a small minority develop later on.

But you must at the same time perceive how completely justified we were in distinguishing tumours from the other progressive disturbances of nutrition—the enlargements resulting from defective consumption, the hypertrophic and inflammatory increase of tissues, and the infective new formations. Nothing but an etiological definition of a tumour can enable us to draw the sharp limitation between hypertrophy and inflammation on the one hand, and tumour-formation, on the other, which the instinct and unprejudiced observation of physicians have repeatedly demanded, and exact investigation, on the contrary, so often obscured. How imperfectly, indeed, the purely anatomical standpoint is suited for the comprehension of the latter process may be illustrated by the case of a comparatively simple, and anatomically well-known, form of tumour, *goitre.* A goitre—we are taught by pathological anatomy—is an enlargement of the thyroid dependent on a homologous increase of its tissues, which at one time involves the whole organ, at another one of its lobes, at a third a portion only of a lobe. It is sometimes, but not usually, associated with exophthalmia and with dilatation or hypertrophy of the heart; may arise epidemically through miasmatic causes or sporadically in the absence of such; often disappears or is reduced by the use of iodine, and, again, often fails to react to this agent, &c. Who could feel any satis-

faction in a definition which cancels in each succeeding clause what it has in the preceding one affirmed? But the matter assumes a very different aspect when etiological principles are applied to it. We then perceive that the thyroid oversteps its physiological limits when the arterial blood-supply remains for a long time abnormally increased. This occurs, in the first place—very probably as the result of a dilator neurosis—in Basedow's disease, and, secondly, in consequence of a miasma, the nature of which is at present unknown, though it is certain that it is confined to certain regions. The abnormal growth results in *a hypertrophy* of the thyroid gland, that disappears when the causes giving rise to it cease to act, *i. e.* when Basedow's disease is recovered from, or the region of endemic goitre forsaken. The abnormal growth undergone by the thyroid in consequence of the presence in it of redundant germinal material differs greatly from its hypertrophy. It, of course, also leads to the production of thyroid tissue, which may, like that of the hypertrophic enlargement, become colloid, but the new tissue assumes the form of atypical nodules, and constitutes, in short, a true *goitrous tumour*. Hence it is that this kind of goitre has no connection with locality or with miasma; never recedes spontaneously, and probably never as the result of iodine treatment; has nothing in common with exophthalmia, &c. Should it turn out—as I am inclined to believe on the strength of some few observations—that Basedow's disease and miasmatic goitre invariably attack the entire thyroid, while the true goitrous tumour perhaps always assumes the form of atypical nodules, we should then, indeed, have secured an anatomical criterion by which it would be possible to distinguish the forms of goitre, so different in their essential nature. Let me be clearly understood to mean a gross anatomical or morphological criterion, for by employing the microscope it would be no less vain to attempt to distinguish a miasmatic goitre from a true goitrous tumour than to separate between, say, a lipoma and true polysarcia.

Still more instructive perhaps is the history of the hypertrophies of the lymphatic glands. These, indeed, display such a want of agreement in their entire course, and as regards implication of the rest of the organism, that the

necessity for drawing definite distinctions between them has long been familiar to the physician. But just make the attempt to discriminate from a purely anatomical standpoint between what are called hyperplasias, lymphomas, and tumours of the lymphatic glands! Even if the swellings ending in suppuration be disregarded you have forms which are strictly local and limited to a particular region. To this category belong the *simple indurative glandular enlargements* following *chronic catarrhal* and other *inflammation*, such as are often seen in the tonsils, cervical glands, &c.; and, in the next place, the *lymphoma* proper, *i. e.* a more or less firm hypertrophy of the gland, which terminates neither in suppuration nor caseation and arises without antecedent inflammation of the tissues of the neighbourhood, and especially of the mucous membrane; it, too, is most commonly met with in the side and nape of the neck. Then we have a number of hypertrophies of the lymphatic glands which are found to affect the lymphatic system more or less widely, sometimes involving all its parts, and which invariably have, at any rate, a tendency to become disseminated. They are *leukæmic hyperplasia, scrofulous* and *tuberculous* enlargements, and *lymphosarcoma.* Of these forms only one is sharply characterised anatomically or readily distinguishable from the others, namely, the *scrofulous,* for which *caseation* is pathognomonic. But who would consent to accept the striking anatomical resemblance of a leukæmic to a lymphosarcomatous gland, or to an ordinary lymphoma, as reason sufficient for identifying these processes with one another,—for identifying them, that is, despite the difference in the constitution of the blood and despite their dissimilar course? Nothing but an etiological conception can, it seems to me, bring order into this confusion. We distinguish (1) an *inflammatory* hyperplasia, the strict analogue of the periosteal thickening of bone or of the pleuritic or the peritonitic thickening of a serous membrane; this is the indurative swelling of the lymphatic glands. (2) *Infective* hyperplasia; to this class belong certainly the *scrofulous* enlargements, in accordance with the conclusions we recently arrived at; further, a portion of the *lymphosarcomata,* and probably also the *leukæmic* tumours. At any rate, if leukæmia is not an infective dis-

ease it is a general affection produced by an unknown agent, which is all that need be granted for our present purpose. (3) *Enlargements depending on the presence of embryonic germs, i. e.* true tumours of the lymphatic glands, the *lymphoma* and some of the *lymphosarcomas.* The two latter essentially resemble each other, and are related the one to the other, like a so-called benign to a malignant tumour: this I shall soon have to explain more particularly. For the rest, I have already pointed out the possibility that careful examination might discover in *the morphological atypia* of the lymphomatous tumours in point of relative arrangement of medullary cords, follicles, and lymph-sinuses, a valuable differential criterion from the infective hypertrophies.

While the etiological conception alone brings clearness and order into this domain, it does more than this; for without it, it would be impossible to distinguish scientifically between certain forms of tumours and the products of inflammation. Nothing is more certain than that periostitis may, and very frequently does, result in the formation of new bone, that in consequence of inflammation fibrous connective tissue is produced in quantity, and that stratified epithelium is at the same time formed in abundance. But is one therefore justified in concluding that wherever newly formed bone, abnormal connective tissue, abnormal tegumentary epithelium, are met with, some inflammatory process, or, as it is called, *a local irritation,* must there have been at work; and that, despite the possible absence of any redness, tenderness, heat and fever? You know that we do not, and why we do not, so conclude. But by what means can an osseous, or connective-tissue, or epithelial tumour be distinguished from an inflammatary product having the same histological characters, when they are compared simply from an anatomical standpoint? Not by atypia; for the most spiny exostosis may not be more atypical than are the needles of callus so often formed during the repair of a comminuted fracture; or a cutaneous horn more irregular than a condyloma acuminatum. Let the object be never so carefully examined, macroscopically and microscopically and also chemically, no differential criterion can be discovered except the *etiology.* This only, and not appearance nor form, determines the nature of a growth.

When a leg becomes enormously thickened as the result of oft-repeated inflammation of the skin and lymphatics, when what is called *elephantiasis* is developed, the affection is, despite the atypia, *inflammatory* ; on the other hand, an elephantiasis of the scrotum or of the nymphæ, setting in in the absence of all inflammation as an hereditary, and even congenital, or racial peculiarity, constitutes a *tumour*. A true *neuroma* is a tumour consisting of nerve-fibres, and developing either singly or multiply in the course of a nerve, without any apparent external cause, perhaps under the influence of heredity; but when, in accordance with the recently discovered principles of nerve-regeneration, the old fibres of the stump of an amputated nerve give rise to a cluster of new ones, which become woven together into a tangled mass, the structure is not a true tumour, in spite of its atypical nodular form.* These examples, which might easily be multiplied, will, I hope, show you that our etiological conception of a tumour goes down to the very root of the matter, and is throughout applicable. For a scientific understanding of tumours our view is therefore not merely justifiable but necessary; and I hope in what follows to prove to you how fruitful the hypothesis also is in explaining the life-history of tumours as well as their pathology in a stricter sense.

Turning now to the *biology* of tumours, it is obvious that one principal aspect of the question—function—may be altogether disregarded. For, in tumours as atypical structures, we know nothing of any such function as characterises all the organs of the animal body. The muscle-fibres of a myoma, smooth or striped, are of course irritable, but owing to the absence of the necessary nerves they are not as a rule excited to contraction, and even were they so excited, they could not, like other muscles, do work, since appropriate attachments are wanting. The adenomata and glandular cancers never secrete, partly because they are not placed in "typical" connection with the excretory ducts, but princi-

* This passage, which occurred word for word in the first edition, shows that the objection of Virchow (his 'A.,' lxxix, p. 190) to my theory, based upon the neuromata occurring after amputation, is without force.

pally owing to the absence of the required innervation; even in the true lymphomas and lymphosarcomas it is more than doubtful whether genuine lymph is ever produced. Our interest is consequently fully claimed by another aspect of the biology of tumours, namely, the discovery of the laws which regulate their *growth and nutrition.*

Yet we have anticipated in our preceding discussions the most important facts coming under this head. You already know, not only that *embryonic germs* form the starting-point for the development of the tumours, but also that the sole positive condition necessary to their development is an *adequate supply of blood.* But the blood-supply must be both quantitatively and qualitatively sufficient; however typical its germ, an osteoma could not develop, unless the blood be enriched with the necessary lime-salts, nor could a lipoma be produced except the indispensable fat-forming substances be absorbed into the organism with the food, and remain in a corresponding measure unconsumed. Moreover, I adduced most striking proofs that a long-continued augmentation of the blood-supply is capable of greatly accelerating and enhancing the growth of tumours. The increase of cartilaginous and bony tumours of the skeleton and of dermoids at puberty, as well as of mammary and ovarian tumours during pregnancy, are facts which have been repeatedly and decisively verified. It has also been positively, though more rarely, observed that an inflammatory hyperæmia was the means of bringing about the development of a rudiment of a tumour; while the belief that a neoplasm may have its growth accelerated by congestive and inflammatory hyperæmias dependent on local irritation is too well attested by the statements of the most eminent surgeons to admit of doubt—even if it be assumed that in many instances inflammatory new formations have falsely been referred to the class of true tumours, that, *e.g.* proliferating granulation-tissue has been mistaken for a round-celled sarcoma. These factors are, however, far from explaining the striking inequalities in the rate of growth of the various tumours. Here conditions, as yet unknown, but certainly inherent in the different tumour-rudiments, must undoubtedly play a part. The period of embryonic life from which the germ is derived may

perhaps be of importance in this respect, growth being more rapid the earlier the stage at which the redundant germ originated. This idea is apparently favoured by the history of the sarcomata, and of the striped myomata of the kidney on the one hand, and of the myomata, fibromata, lipomata, and osteomata on the other. Lastly, we need not again recur to the question of *conformation* in the growth of tumours; for we found an essential support for the theory of embryonic rudiments in the fact that the tumours, while retaining the histological characters of their germs, display a more or less distinctly marked but always perceptible *morphological or histological atypia,* as compared with the organs and tissues of the fully-developed body.

The *metabolism* and *nutrition* of the tumours may also be dismissed with a few words. For since—in addition to the conditions inherent in the germ—the circulation is the only factor influencing the metabolism of tumours, the processes of nutrition are in them less complicated than in perhaps any of the physiological organs. In all pseudoplasms except the very smallest, blood-vessels are present; these are formed and grow precisely as in the organs and tissues during physiological growth, but with this difference, that *the vascularisation of tumours is atypical.* Hence it happens that they are now poor, now rich in vessels—a variation which holds not only of different kinds of tumours, but of those too whose structure is in other respects identical. Myomas, fibromas, myxomas may in some cases be very poor in vessels, in others so abundantly supplied with them that they acquire an actual *teleangiectatic* character; nay more, within one and the same tumour the greatest differences as regards vascularity occur. Further, the relative proportions of the *different kinds of vessels* is very often completely atypical in tumours. At one time the capillary vessels preponderate very decidedly; at another the venous system is chiefly developed; while the tumours of the third group are distinguished by such an abundance of arteries that they pulsate *in toto.* And, lastly, to complete their atypical character, the structure of the individual vessels often deviates from the normal; fusiform or cylindrical *aneurysms, phlebectases,* and more especially *ectases of the capillaries* occurring in soft tumours, are matters of

everyday experience. It need hardly be said that these conditions do not exclude, but rather favour, local disturbances of the circulation. Thus tumours are liable to all the well-known increases and decreases of resistance, to anæmias, to congestive and stagnative hyperæmias, to thrombosis and embolism, to hæmorrhage and inflammation, and it is by no means uncommon to find the course and history of the tumour very essentially influenced by such circulatory disturbances. This result is chiefly brought about through the influence exerted by these disturbances on the metabolism of the elements of the tumour; and that it is so I need hardly prove, as we have more than once selected tumours in illustration of the various kinds of nutritive derangements. You may remember that I spoke to you of the frequent occurrence of fatty change in neoplasms, both in the rapidly growing—local embonpoint—and in the older, less vascular growths—fatty atrophy. I also referred to the *calcification* of old myomas and fibromas, when dealing with the view that the lime salts contained in the transudations are deposited by preference in obsolescent parts. Nor did we forget the *colloid* degeneration of tumours. These are all undoubted derangements of nutrition; while the ossification of enchondromata and of fibromata of the periosteum, already alluded to, as well as the *fatty changes* occurring in mammary cancers and adenomata, and the *cornification* of the cells in cancroids do not so much constitute pathological degenerations as regular developmental stages of the respective tumour-rudiments. The influence of the degenerations on the subsequent history of the tumours need not be specially discussed. While the calcification of a tumour may generally be taken as indicating that it has ceased growing, you are no doubt fully alive to the fact that it is not the calcification as such, but the presence of conditions admitting of it, that warrants the favourable prognosis. The occurrence of fatty atrophy is also on the whole not unwelcome, since it often inaugurates a partial or general diminution of the tumour; where umbilicated depressions of the surface of a growth point to an antecedent reduction in bulk, you may as a rule assume that a fatty, and not a simple atrophy, has there taken place. But by far the weightiest and most significant of the nutritive

derangements met with in tumours is the *necrosis* to which many varieties are very liable, probably because the atypical, irregular circulation has been from the first unfavourable to the nutrition of their cellular elements. Necrosis, by attacking the tumour *in toto*, may occasionally lead to its complete destruction and thus prove a most desirable accident; but very much more commonly it is a most unwelcome and dreaded event, especially where the tumour borders on a surface, for it is then inevitably followed by *ulceration* with all its attendant inconveniences and dangers.

In what I have just told you of the process of nutrition in tumours and its derangements, you will have noticed much that indicates their subsequent fate, yet still more remains to be said before we have answered the question—*What is the ultimate destiny of a tumour?* And yet this is the cardinal question in the pathology of tumours, since only by replying to it do we arrive at a conclusion as to the importance of these growths for the organism. True, the problem is more easily stated than solved; or rather, its solution is impossible when thus generally enunciated. For in the life-history of tumours, there is only one universally applicable fact, namely—*that a neoplasm never spontaneously recedes and disappears.* The elimination, rarely occurring after antecedent necrosis, can no more be termed spontaneous resolution than can the separation of a gangrenous foot; and though fatty atrophy may reduce the volume of a tumour, we do not know that it has ever resulted in complete spontaneous healing. This *persistence* of tumours is, moreover, easily understood on our view. A miasmatic goitre becomes retrogressive when the miasma is eliminated from the body; a syphilitic new-formation heals, though usually after forming a cicatrix, when the activity of the syphilitic virus is finally destroyed or at least temporarily in abeyance. But if, as we believe, the true neoplasms originate in germinal embryonic material, I cannot imagine how, or by what means, a spontaneous retrogression could be effected. No kind of work is done in the tumours at the cost of their own substance—work such as probably causes the atrophy and final disappearance of the thymus when the physiological apposition of new thymus-cells has ceased. If, however, we neglect this com-

mon character of persistence, it is hardly possible to imagine greater differences than are actually observed in the life-history of tumours. Some of them—*e.g.* many fibromas, lipomas, exostoses—remain stationary for years or during the whole of life without at any time exceeding moderate dimensions. Others of exactly similar structure grow, slowly indeed, but *continuously*, finally attaining an enormous bulk. Thus lipomas and fibromas of from thirty to forty pounds in weight are nothing rare; equally large uterine myomas have repeatedly been observed; and elephantiasis of the scrotum is stated sometimes to result in the production of tumours weighing more than a hundred pounds. Moreover the majority of tumours, whether small or large, remain localised and strictly limited to the region and tissue where they have from the first developed. A very considerable number, however, are not at all, or only temporarily, circumscribed, and extend as they grow into neighbouring tissues, or even give rise to the production of numerous similar tumours in regions lying more or less remote. I need hardly say that the two properties last named—the implication of *the tissues of the neighbourhood* and *the formation of metastases*, also called *generalisation*—constitute the differential criteria of the malignant tumours.

Inquiring now into the causes of these surprising differences in the history of the pseudoplasms, we find that scarcely any attempt has been made to explain the fact that the growth of tumours identical in kind is at one time moderate, at another almost unlimited. To reconcile these differences on the traumatic, or still more on the infective theory, would indeed be difficult. Nor can I offer you more than a hypothesis; yet it follows almost as a necessary inference from our theory either that the embryonic rudiments are from the first unequal in size and hence possessed of unequal capabilities for growth, or that the cause of the difference in growth is to be sought in the meagre or abundant supply of material, *i.e.* blood-supply. That the vigorous growth of many, previously small and stationary, tumours at certain periods—at puberty, during the period of most active development of the skeleton, during pregnancy, or as the result of congestions depending on other causes—makes decidedly

in favour of the second alternative, is obvious; yet in many other cases the first may exert its influence. Much more stress is usually laid on the question of the *central* or *peripheral growth* of a tumour; understanding by central growth one *resulting from the multiplication of the tumour-elements themselves*, and by peripheral an enlargement of the tumour *by a new formation proceeding from the tissues surrounding it.* Now you see at once that this distinction is meaningless if the tumours do not originate in the fully-formed tissues of the part, that it is worthless on our hypothesis. For if, as we think, tumours develop from embryonic germs, *a peripheral growth in the above sense does not take place.* Hence we have no need for a special term to describe their mode of growth, since it is in all probability identical with that of physiological tissues. Nevertheless, when a structure is so atypical as are all tumours, its relation to the substratum in which it grows may vary. In this regard, a distinction has long been recognised between tumours which stand out more or less sharply against neighbouring structures, and those which, without any clear boundary, are *diffuse*, and become lost in their environment. Which of the two conditions will be present depends chiefly on the nature of the tumour in question. A simple lymphoma must of necessity be as sharply marked off from the surrounding connective tissue as is the lymphatic gland in which it has originated; and it is evident that growths which have developed from so-called aberrant germs, such as the adenomas of the axilla and the enchondromas of the parotid region, will remain circumscribed, so long at least as they run a benign course—of which more anon. On the other hand, every purely epithelial tumour growing on an epithelial membrane must obviously be more or less diffuse, since there is no tissue between the epithelial cells, by the agency of which a limitation might be brought about. Not so in those tumours which are partly composed of connective tissue, and originate where connective tissue exists. Both alternatives are then possible; we meet with circumscribed and with diffuse lipomas, fibromas, angiomas, &c.; and it often enough happens that a lipoma or a fibroma, an angioma or a smooth myoma, after having for a long time grown diffusely, gradually stops short

and becomes defined against the tissues of the part, and is at last circumscribed. In many cases this is a purely mechanical effect, as when a myoma or fibroma grows like a polypus from the uterus or the skin, the connection with the substratum becoming more and more reduced. It may also happen that a tumour, having ceased to grow, becomes surrounded with a kind of connective-tissue capsule, like that of cysticercus, &c. From all this you perceive that no fundamental importance *can* attach to the existence of a sharp or of a diffuse boundary between a growth and the tissues of the substratum ; and it is likely that less stress would have been laid on the distinction had it not a practical value in operative surgery. For *total* extirpation is not only much more easily but much more certainly effected in circumscribed than in diffuse tumours; and since, for obvious reasons, nothing but the complete removal of a tumour (with its germs) will secure against a renewed growth from any elements that might remain, and thereby against a *recurrence*, it is not difficult to see why surgeons have regarded the circumscribed or diffuse limitation of a tumour as distinctive characteristics requiring to be noted.

True, we have not as yet considered a factor which cannot be neglected in any attempt to discover the conditions and laws of the growth of tumours, namely, the *influence exerted upon the neoplasm by the tissues in its vicinity*. As regards physiological development, it has been known since the earliest period of scientific embryology that the size and conformation of each part of the body is the product of the interaction of all its growing tissues. Do similar conditions influence the growth of the pathological tumour-rudiments? A *positive determining* influence on the form and structure of a tumour cannot proceed from the tissues of its environment, simply because the growth of the latter is determined solely by physiological laws, and has nothing in common with that of the tumour-rudiment. This, and this alone, has the conditions of *abnormal* growth in itself. But whether the tissues of the neighbourhood may not be influential *in checking* the growth of a tumour is another question. Such an influence is certainly conceivable, especially on the supposition that the physiological tissues by which the tumour-rudi-

ment is surrounded make, for purposes of growth and nutrition or for the discharge of their functions, such demands on all or the greater part of the nutritive material conveyed by the blood-vessels that the remainder does not suffice for the development of the tumour-rudiment. This hypothesis makes it easy to understand, for example, why the decided majority of all true tumours are observed in advanced life, at a period, that is, when the activity of physiological growth and regeneration has been considerably lowered, and the specific functions are performed with lessened energy. This, you perceive, is something very different from the *alleged arrest in a mechanical sense*, the influence of which on the growth of a tumour is in my opinion infinitesimal or *nil*. For growth is an enormous force, and while it is now and then observed that a sarcoma or a medullary cancer suddenly begins to enlarge with rapidity when the skin is broken through, it is incomparably more common to find that the skin in no way hampers a tumour in its growth. A tumour of any kind, hard or soft, an osteoma as well as a lipoma, a fibroma or a myoma as well as a goitre, may attain enormous dimensions; the superjacent skin, or muscles, or serous membrane being utterly helpless to prevent this. All the tissues are *shoved aside and separated* by the growing neoplasm; muscles, nerves, and vessels are flattened; the cartilaginous trachea is displaced and *narrowed*; even a dense tissue like bone cannot withstand the pressure of a fibroma, a mediastinal goitre, or a teratoma, and becomes eaten away from pressure-atrophy. While, then, *mechanical resistance* from the tissues of the neighbourhood cannot properly be regarded as an obstacle to the growth of a tumour, this is very far from true of what may be called the *physiological resistance*. Nor are we here indulging in mere speculation, for normal embryology most positively teaches that *the reciprocal boundaries between the tissues are never infringed*. The nerves never grow into the muscles nor into the skin, but certain cells in these portions of the embryo become differentiated into nerves. As regards the glands, thoughtful embryologists have long been aware —at any rate long before Boll's time—that they arise by the approximation and mutually advancing growth of vascular connective tissue and epithelium, and not by the in-

growth of epithelial cells into vascular connective tissue. Is it possible that a principle so important and generally applicable as this should not hold good also of the embryology of tumours? To the great majority of tumours it applies fully; however vigorous their growth, whether sharply or diffusely bounded, they press aside and compress the neighbouring tissues, and even cause an extreme degree of atrophy in them; but they invariably halt at the borders of the foreign tissue, and never penetrate into it. Yet in a number of growths—the *malignant* tumours—this principle is utterly inapplicable. These tumours, as I already pointed out, ruthlessly invade the neighbouring tissues; nay more, secondary growths in remote localities, which present the greatest physiological differences, may arise under their influence.

In thus taking the criterion of malignancy to consist in *the falling off of the physiological resistances* in the parts bordering on, or remote from, a tumour, I come into conscious collision, it must be confessed, with the notion of malignant tumours which has till now been in vogue amongst pathologists and surgeons. As to the characters comprised under the term malignancy there is no difference of opinion, but the cause of the ruthless local extension and of the generalisation is sought, not in the behaviour of the organism, but *in the properties of the tumour itself.* From this point of view attention was specially directed to the conformation and histological structure of tumours running a malignant course. And it turned out that the vast majority of them follow the *epithelial* type—*carcinoma* or *cancers* in a strict sense; or the *connective-tissue* type—*sarcomas.* Hence pathologists have come to identify the notion of a tumour running a malignant course (a cancer in the general sense) with the forms of sarcoma or carcinoma, so much so that even in cases where a tumour, after long remaining stationary, takes a malignant turn, *a carcinomatous or sarcomatous degeneration of the tumour* is said to occur.

However, it is not difficult to discover the weak points in such a position. And first of all as to *carcinoma*—this name is given, as you know, to tumours *consisting of a connective-tissue framework or stroma carrying the vessels, in the meshes of which epithelial cells are embedded.* Now a moment's con-

sideration will show that the criteria of malignancy are already implied in this definition; for, since the carcinomas originate in epithelial germs, the existence of a connective-tissue stroma would be altogether impossible had not the tumour in growing already implicated the foreign heterologous tissue. Accordingly the rule that a great number of the malignant tumours are distinguished by a carcinomatous structure is simply equivalent to saying:—for a number of the malignant tumours their malignancy is characteristic. The object is not to explain that the carcinomas are malignant and run a malignant course, but to show how it happens *that some epitheliomas and adenomas run an unusual course*, viz. a *malignant* one. But how as regards the *sarcomas?* These are not *per se* suspicious or remarkable tumours; rather they are, as we have seen, the descendants of redundant germinal material originating at a very early period: wherein then consists the cause of their malignancy? If, indeed, the sarcomas *as such* were always malignant tumours, our view of what constitutes malignancy could not be exhaustive. Happily they are not so. The sarcomas are originally no more malignant than the adenomas, and *a very considerable number of them do not even become so during the whole of life.* The pathological anatomist often enough discovers by chance in some body examined by him a genuine spindle-celled sarcoma of the dura or of the pia mater; and if it be objected that in such cases it is impossible to say whether the tumour has long been present or not, I refer you to the *sarcomatous epulis,* which may attain a considerable size and even grow rapidly, and may recur repeatedly after imperfect extirpation, but *never becomes generalised.* Sarcomas of other bones; further, of the ovaries, mediastinum, fascias, &c., may exist for several years, causing severe disturbance owing to their gradually increasing dimensions, and yet may *never penetrate into foreign tissues or give rise to metastases.* Even in those sarcomas, the subsequent course of which is marked by extreme malignancy, there is always, as Virchow* truly observes, an antecedent *period of innocency*—to my mind, a most convincing proof *that it is not on the nature of the tumour that the malignancy depends.*

* Virchow, 'Geschw.,' ii, p. 266.

And now consider in addition those remarkable cases which at first had the mere interest of rarities, but which have been recorded during the last ten years in increasing numbers—those cases, namely, where tumours generally displaying perfectly benign characters run an exquisitely malignant course. The earliest recorded and most celebrated cases were examples of malignant *enchondromas* with metastases;* at present, however, the tumours in which a malignant course has not been observed are actually in a minority. The enchondromas were followed by the myxomas, of which you will find a number of examples in the works of Virchow and Lücke on tumours.† Malignant myxolipomas‡ have repeatedly been met with, and we are in possession of some observations on malignant fibromas§ by trustworthy writers. Then it is by no means uncommon for gliomas of the retina to assume intensely malignant characters.|| Even comparatively highly organised tumours supply their contingent; *e. g. smooth and striped myomas*¶ and *ovarian cystomas.*** I had recently myself an opportunity of observing the generalisation of ordinary colloid goitre.†† You perceive that all sorts of tumours, hard and soft, fibrous and cellular, may become generalised; and this, you will notice, *without any change in histological structure* or chemical constitution. The only possible conclusion to be drawn from all this, so far as I see, is—*that it is not the characters of the tumour that determine the innocency or malignancy of its course.*

This being so I feel compelled, as already hinted, to advance and defend the theory that the benign or malignant character of a tumour depends solely *on the behaviour of the remainder of the organism.* The physiological resistance in

* Virchow, ibid., i, p. 499; Lücke, l. c., p. 160.

† Virchow, l. c., i, p. 432; Lücke, l. c., p. 174.

‡ Waldeyer, 'Virch. A.,' xxxii, p. 543; Virchow, ibid., p. 545; Lücke, l. c., p. 175.

§ Paget, 'Lect. on Surg. Path.,' ii, p. 151; R. Volkmann, 'Bemerkungen über einige vom Krebs zu trennende Geschwülste,' Halle, 1858.

|| Knapp, 'Die intraoculären Geschwülste,' Carlsruhe, 1868; Schiess-Gemuseus u. Hofmann, 'Virch. A.,' xlvi, p. 286; cf. especially Leber, l. c.

¶ Eberth, 'Virch. A.,' lv, p. 518; Brodowsky, ibid., lxvii, p. 227.

** Maygrier, 'Meeting of the Paris Soc. anatom.' of 7 Febr., 1876.

†† Cohnheim, 'Virch. A.,' lxviii, p. 547.

the vicinity of a growth must, I think, be diminished in order that a tumour may become locally malignant; and similarly, there must be a falling off in the physiological resistances of the other tissues of the organism for a tumour to become generalised. But before proceeding to the detailed consideration of the evidence in favour of this view, it will be well that you should have a more accurate acquaintance with the facts, more especially of generalisation.

There are, as is well known, several modes of generalisation. Of these the commonest, as well as decidedly least pernicious, is that by way of the *lymph-stream.* In one of the lymphatic glands lying nearest the original tumour an analogous growth arises; thereupon another gland of the same group becomes involved, and then yet another; others situated more remotely in the direction of the lymph-stream finally follow, till complete chains of cancerous lymphatic glands, extending it may be to a great distance, are formed. Meanwhile the larger lymphatic vessels usually remain unaffected; still in the stomach, intestines, lungs, and elsewhere, the lymphatics themselves are often found as thick, beaded cords plugged with masses of tumour. To the same category belongs the eruption of metastatic nodules *in the serous membranes,* the peritoneum, the pleura, and the pericardium; for the serous cavities are, as you know, lymph-spaces, and consequently portions of the lymph vascular system. In a second form of generalisation, on the contrary, the lymphatic system is not involved. Nodules may then arise indifferently in any organ, without geographical, histogenetic, or functional relation to the seat of the original tumour. The parts decidedly the most liable to *tumour-metastases* are the *liver* and the *lungs;* yet there is really only one tissue—*cartilage*—in which they do not occasionally occur. In all the other tissues—subcutaneous fat and bone; skin and muscles; kidneys, spleen, testicles, ovaries, pancreas; brain and thyroid body; fibrous and serous membranes; heart and uterus; all mucous membranes; choroid and iris—in all possible places, in short, one must be prepared to meet with tumour metastases. Obviously they may occur too in lymphatic glands which draw their lymph neither from the primary tumour nor from any of the organs containing metastatic nodules. There

appears to be no rule as to the localities, organs, or tissues in which metastases develop, and at any rate I should not be willing to subscribe to the law formulated by Virchow*—that the organs more especially predisposed to the formation of primary tumours present a very slight tendency to metastases, and conversely. For while this is indeed true of the liver, lungs, heart, and serous membranes, on the one hand, and of the uterus, stomach, and eye on the other ; the bones, lymphatic glands, and subcutaneous cellular tissue, as well as the brain and its membranes, are, as Virchow himself has noticed, about equally subject to primary and to secondary tumours. In my opinion, then, a mutual local exclusiveness between primary and secondary tumours, such as Virchow's law would indicate, does not exist ; and while one or the other is chiefly met with in certain organs, the cause of this predisposition must certainly be sought in some other direction. In a third class of cases, generalisation by the lymphatic system is combined with metastasis in the strict sense ; and then, as a rule, the affection of the lymphatic glands precedes the formation of metastases by a longer or shorter interval.

In considering the mode in which the generalisation of tumours is effected, one fact must be kept prominently in view, that is, the *agreement of the secondary with the original tumour* in histological structure and in chemical constitution. So complete is this agreement throughout that it is very often expedient, when studying the structure of a malignant growth, to examine the metastases rather than the primary tumour—if, for example, the latter has undergone considerable alterations in consequence of hæmorrhage, or of necrosis and ulceration. True, the metastases may and will display a marked departure in form, and often acquire greater dimensions than the primary tumour. Yet these differences are of so little importance as compared with the identity of internal structure, that the actual *dependence* of the secondary nodules on the primary growth admits of no shadow of doubt. *The secondary tumours arise because a primary one is already present.* This conviction led to the theory that *an infective material* is produced in the primary tumour ; that this mate-

* Virchow, 'Geschwülste,' i, p. 69.

rial becomes disseminated from the infective focus, partly through the tissues in its vicinity, and partly throughout the entire body, by means of the lymph- and blood-streams; and that it gives occasion to the production of new but similar tumours. *The virus*, you will note, *is capable only of infecting the organism in which it is produced, and no other.* Accepting with this reservation the theory of infection as a simple expression of the facts, it is evident that the infective agent must either be a substance soluble in the juices of the tumour and the body, or have a corpuscular character; and if the latter, that the histological elements of the tumour can alone come into question. In choosing between these alternatives, we shall be influenced by an objection already met with (vol. i, p. 309) when considering the localised infective diseases, namely, whether a soluble agent dissolved in the fluids of the body could be the cause of, *e.g.* the infective inflammations. And I must confess with respect to tumours that I find it impossible to conceive in what way a substance dissolved and circulating through the body could produce effects which are strictly circumscribed, and that not only in the organs in which it is separated but in all possible parts of the body. Neither am I acquainted with any facts which compel one to such a conclusion. Stress has been laid on the circumstance that the *juiciest tumours* most easily become generalised, but it is in these tumours that the cellular elements are without exception most abundant. And to the objection that the size of the cells of many metastases would prevent their passage through the blood-vessels or lymphatics, it may be replied that the cells may have become larger after their settlement in the new locality. Friedreich's* well-known case, from which the advocates for infection by the juices derive their chief support, may be explained in another way. In it a cancerous "metastasis" developed in the left knee of a fœtus, the mother of which perished from a cancer of the liver that was first noticed and became widely generalised during the pregnancy. The patellar tumour I hold to have been *a hereditary cancerous growth which had originated during embryonic life and was therefore congenital*; in the belief that it was *not a metastasis* I am strengthened by

* Friedreich, 'Virch. A.,' xxxvi, p. 465.

the fact, expressly noticed by Friedreich, that *the cancer cells were smaller* than those of the maternal tumours. On this interpretation, the possibility of which you will not dispute, the case is of no importance as evidence for the hypothesis of infection by the juices.

It is very different with the theory which attributes the infection *to the transport of tumour-elements.* To render this theory acceptable it is indeed necessary to show not merely that the elements of tumours frequently enter the lymphatics and blood-vessels but that, having been conveyed by the lymph- or blood-stream to some part or other of the lymph- or blood-vascular systems they may there undergo further development, viz. may multiply and grow to form large nodules. Now with regard to the first postulate, such an amount of evidence has been accumulated in recent years that it has ceased to be a subject for controversy. We have stated that the larger lymphatics may often be seen by the naked eye to be plugged with masses of tumour; but the principal gates of entrance are not the macroscopic but, as demonstrated by Köster,* the microscopic lymphatics. These latter channels play such a part in the local extension of many cancerous growths that, for example, the conical, clubbed, and linear forms assumed by the cell-masses in cancroid are determined solely by them. But the penetration of malignant tumours into the blood-vessels is also an extremely common event. It is chiefly the veins, both large and small, that are attacked by the malignant tumours; these first involve the walls and after a time press forward into the lumen itself. An examination of rapidly growing tumours of marked malignancy, if carefully carried out, will reveal, perhaps in the majority of cases, some vein into whose lumen there projects a parietal, often fungus-like, thrombus, consisting exclusively of tumour-elements or of a mixture of these with blood. But how many growths must penetrate the microscopic vessels—the capillaries and smallest veins! For the rest, will you bear in mind that the lymph-stream may be the means of conveying tumour-elements into the blood-vascular system.

* Köster, 'Die Entwicklung d. Carcinome und Sarkome,' Heft 1, Würzburg, 1869.

The second of the above postulates is rather more difficult to establish. The possibility of the *transport* of particles from a tumour by the lymph-stream to the lymphatic glands and by the blood-stream into distant parts of the vascular system is, it is true, unquestionable; endless opportunities offer for observing typical *emboli*, which consist of masses of tumour. But the uncertainty of the inferences that may be drawn from the discovery of a cartilaginous embolus in the midst of a metastatic pulmonary enchondroma, or of a cancerous embolus of the portal vein in secondary carcinoma of the liver is most strikingly evidenced by the dissension prevailing amongst writers as to the mode of development of the metastases in question. According to one party,* there takes place a kind of infection by the cancerous embolus of the arterial wall and its vicinity, which enables the latter themselves to produce a cancerous nodule; according to another,† the cells of the embolus constitute a new germ, from which the metastasis grows, just as the primary tumour grows, on our view, from embryonic germinal material. Except by having recourse to experiment, it cannot in my opinion be decided *whether a fragment of tissue set free from the substratum in which it has grown is really capable of producing fresh tissue in the interior of a vessel* after becoming arrested in it. Experiments directed to this end were not long since carried out by Maas and myself.‡ Pieces of periosteum were taken fresh from the tibia, and introduced through the jugular vein of rabbits, dogs, and especially hens, into the ramifications of the pulmonary artery. *The result of these experiments was a positive one.* The pieces were supplied with vessels (just as is a simple thrombus) from the vasa vasorum of the artery in question, and within two weeks produced *first cartilage and then ordinary typical bone,* the vessel-wall having taken no other share in the process. Accordingly it may be freely admitted as possible that particles torn off from a tumour, and afterwards becoming arrested, may go on growing independently; while as regards the secondary develop-

* Virchow, l. c., i, p. 55; C. O. Weber, 'Virch. A.,' xxxv, p. 501; Klebs, Prag. Vierteljahrschr.,' cxxvi (p. 15 des Sep.-Abd.); Gussenbauer, 'Virch. A.,' lxiii, p. 322; (Prager) 'Zeitschr. f. Heilkunde,' ii, p. 17.

† Bizozzero, 'Molesch. Unters.,' xi, p. 50; Andrée, 'Virch. A.,' lxi, p. 383.

‡ Cohnheim u. Maas, ibid., lxx, p. 161.

ment of cancer in the lymphatic glands, we may accept the view of those authors,* according to whom the growth is effected solely by the multiplication and proliferation of the cancer-cells conveyed into the gland by the v. afferentia, and without active participation of the elements of the gland.

But these experiments led to another result, whose significance I would estimate as broader than that of the former. Not only did the newly formed osseous plates never exceed the limits set by the vessel-walls, but *always without exception disappeared during the next few weeks.* In the fourth week after the introduction of the periosteum we usually met with only small firm rudiments, and never after the fifth week did we find even a vestige of the plug of periosteum. How this total absorption is brought about I cannot say, but you will notice that the fate of the periosteum here is precisely that which it always finally undergoes when transplanted into the subcutaneous tissue, and which overtakes inoculated masses of cancer, even when these have grown exuberantly at the start.† The spur of a cock when transplanted to the comb may attain colossal dimensions; from the root-sheath of a hair implanted upon a granulating wound a considerable growth of epithelium may extend over the surface of the granulations. Even in the anterior chamber of the eye, between the cornea and iris, quite respectable growths have been observed by Goldtzieher and Schweninger‡ to proceed from living particles of tissue introduced into it, though the permanence of these growths is not altogether free from doubt. *But these new formations never penetrate into the tissues of the animals inoculated;* and if the particles be inserted deeply into the granulations, whatever portions of them are capable of absorption disappear. And why does this happen? *Because the foreign particles are incapable of*

* Bozzolo, 'Annal. univ. di Medic.,' 1876, No. 1; Afanasieff, 'Med. Ctbl.,' 1876, p. 212.

† Langenbeck, 'Schmidt's Jahrb.,' xxv, p. 99; O. Weber, 'Chirurg. Erfahrungen u. Untersuchungen,' p. 259, Berlin, 1869; Billroth, 'Wien. med. Wochenschr.,' 1867, No. 72; Lebert und Wyss, 'Virch. A.,' xl, p. 532; Doutrelepont, ibid., xlv, p. 501; Virchow, 'Geschwülste,' i, p. 87; 'Arch.,' lxxix, p. 188.

‡ Goldzieher, 'A. f. exp. Path.,' ii, p. 387; Schweninger, 'Zeitschr. f. Biol.,' xi. p. 341.

withstanding the metabolism of the physiological tissues. I am very far from claiming that this formulation affords an explanation of the fact now under discussion. An explanation would be in any case impossible, so long as the morphological changes taking place during absorption are unknown. My desire is simply to give definite expression to a fact, the knowledge of which supplies, as I hold, the key to the comprehension of the malignant tumours.

For if the physiological tissues of the organism oppose an insurmountable obstacle to the penetration of heterologous cellular material, however capable of growth this may be; or can rid themselves of the presence of such when it is artificially introduced; it seems to me to follow inevitably therefrom that tissues which allow of the penetration of tumour-elements, as well as of the further development and growth of particles carried off from a tumour, *do not behave physiologically*. The tissues may otherwise be quite normal in histological and chemical constitution, but they lack that property which I have already called *the physiological capacity for resistance*. I have repeatedly and unhesitatingly admitted my inability to define this want more precisely; and should any of you, dreading an unknown something, prefer to speak of a certain "feebleness" of the tissues, I shall raise no objection whatever. At any rate, now that we have arrived at an understanding as to the facts, it appears more important to determine the circumstances and conditions in which this feebleness, or incapacity for resistance, of the tissues sets in.

In this connection *inflammatory processes* must, it seems, be given a prominent place. The experiences, lately referred to (vol. ii, p. 723) of C. Friedländer and others with regard to the so-called *atypical proliferation of epithelium* speak unmistakably for the possession by proliferating epithelium of a capacity to penetrate into connective tissue altered by inflammation, or for a power of mutual interpenetration. Waldeyer,* moreover, has with reason called attention to the frequency with which inflammatory changes may be observed in the connective tissue bordering on a cancer. The causes of these inflammatory processes may of course differ greatly;

* Waldeyer, 'Virch. A.,' lv, p. 152.

and hence to reject the possibility that traumatic agencies may in certain circumstances result in the transformation of an ordinary into a malignant tumour is still further from my thoughts than was the denial of their influence on the growth and development of the tumours. Greater importance appears to attach to *advanced age,* as bearing upon the subject now occupying our attention. Thiersch,* as is well known, was the first to lay stress on the importance of this factor for the etiology of cancroid. He pointed out that in old age the connective tissue of the body atrophies, and is consequently no longer capable of opposing the ingrowth of the cutaneous epithelium, which maintains to the last a greater vitality and continues to produce cells. Now I need hardly say that this view, which has besides met with the approval of clinicians generally, commends itself to me not simply as fitting the facts, but as deserving of generalisation. Not only between cutaneous epithelium and connective tissue but, as I believe, in all places where cellular material possessing a vigorous power of proliferation comes into contact with the aged tissues of the body does this relation prevail. It is indeed an old-established rule, though not without exceptions, that the carcinomata do not make their appearance till after the fiftieth year of life ; and if we translate this into our language and say that epithelial tumours do not become malignant before this period, this simply means that one of the signs of senile decay of the body is the feebleness of its tissues or their lessened physiological capacity for resistance.

Still there remains a large number of cases of malignant tumour, to explain which we cannot have recourse either to antecedent inflammation or to advanced age. Inflammation can at best elucidate local malignancy ; and as for age, not only have cases of genuine carcinoma been observed in young, even very young individuals, but the most malignant sarcomas are in the majority of instances confined to the period of youth. Moreover the malignant gliomas are exclusively met with in early life. Upon what the reduction or abeyance of the physiological tissue-resistances depends in these cases, I am utterly unable to say. It is possible,

* Thiersch, 'Der Epithelialkrebs, namentlich der Haut,' Leipzig, 1865.

nay probable, that here too *heredity* plays a part;* but that it does not always participate is certain. I think it best then to declare openly that we are ignorant in many cases of the causes of this feebleness of the tissues. Here is the only point in the entire pathology of tumours at which we are forced to take refuge in an unknown and vague predisposition. On our view predisposition to a tumour is no more to be recognised than is for instance a predisposition to red hair or to a crooked nose. But in order to explain the malignant course of a tumour we cannot dispense with such an assumption. What renders this predisposition especially interesting, and proves at any rate that it is connected with the constitution neither of the blood nor of the nervous system, but only and solely with that of the tissues, is the fact that it sometimes appears to be associated with particular organs and tissues only. This, at least, seems to me to afford the simplest explanation of those remarkable, and far from uncommon, cases, where the metastases are all of them strictly confined to a single system, be it the skin, the skeleton, the intestine, or the lymphatic glands; the system selected having no local, genetic, or functional relation to the seat of the primary tumour. Or is it to be supposed, for example, that all the particles set free from a carcinoma of the breast are conveyed only to the skeleton, yet into all the bones composing it; or that the fragments of a sarcoma of the choroid are all carried to the intestine?

These are the fundamental points—some of them unfortunately hypothetical—out of which the history of the malignant tumours may be constructed. Of the two things which in combination constitute carcinosis, one—the tumour—depends upon embryonic causes: the other—the incapacity of the tissues for resistance—may be congenital, but it is mostly acquired, and very often not till late in life. Hence the course of a malignant tumour may as a rule be divided into *two stages*—an antecedent benign, and a subsequent malignant stage. As a matter of fact, these stages can with certainty be made out in the great majority of malignant

* Thus Broca reports the inheritance of carcinomas in different parts of the body through four generations of one family; quoted by Billroth, 'Krankheiten der Brustdrüsen,' 1880, p. 139.

tumours; and where this is apparently impossible, either the primary tumour has escaped recognition in the benign stage, owing to its obscure position and the absence of symptoms; or—as often happens in cancer of the skin—the tumour is so small and insignificant during the benign stage as not to attract attention till it commences growing into the tissues of the vicinity, viz. becomes malignant. That cancers of the skin should so often escape notice in the first stage is certainly due in part to the necessarily feeble growth of an epithelioma without vessels, rapid growth being impossible till the epithelium has penetrated into the vascular connective tissue. But it is partly explainable from the circumstance that *among the cancroids have been classed a number of ulcerative processes, which,* in my opinion, *are not tumours,* and should, despite a certain similarity, be carefully distinguished from them.

For on reflecting that every stratified epithelium has an inherent capacity for continued cell-production, and that this productive power is augmented by hyperæmia, it will at once be apparent that, even *without the co-operation of an epithelial germ,* the cells of an epithelium may penetrate into the connective tissue, when the resisting power of the latter is destroyed, owing to a trauma, advanced age, or other cause. This is in the main the view of Thiersch, who consequently does not for ordinary cancroid assume the existence of an embryonic germinal material. The atypical epithelial growths of Friedländer also demonstrate this fact in the clearest possible way; for who could entertain the idea that embryonic germs have a share in the production of cirrhosis of the liver, interstitial pneumonia, &c.? And now consider that the same histological appearances must result when normal epithelium penetrates the connective tissue, and when an entrance is effected by the offspring of a redundant embryonic germ—and you will admit that it may be difficult enough to distinguish between the two processes, though they differ so essentially in their nature. Still there are a number of indications which generally enable one to distinguish between genuine *epithelioma* and *cancer-like induration* or *ulcer.* Above all, growth and local extension will be more vigorous and rapid in true cancer, *i. e.* the malignant tumour, than in

the other process; and if you have actual nodules projecting above the surface of the skin you may generally venture on the diagnosis—"tumour." In the next place, the cancer-like ulcer can hardly lead to metastases; for it would be necessary to their production that the physiological resistances should be reduced in remote organs, which need not be anywise affected in, say, the atypical epithelial growth dependent on inflammation; and it would also be necessary that the epithelial fragments torn off and transported should be possessed of a considerable capacity for reproduction, such as does indeed distinguish the offspring of an abnormal embryonic germ, but is scarcely a property of ordinary epithelium. But who will not be here reminded of the slowly spreading ulcerations of the face and portio vaginalis, which, though evidently carcinomatous in structure, penetrate so little into deeper tissues, rarely involve the lymphatic glands, never give rise to regular metastases, and after extirpation do not even always recur?* That they may recur I am the less disposed to deny, as this capacity for local recurrence is only too intelligible from our point of view. In the same category—*superficial cancer of the skin* or *ulcus rodens*—should, in my opinion, be placed some of the cancroids usually referred to as convincing proofs of the traumatic etiology of tumours. I refer to the *scrotal cancer of chimney-sweeps*, and to the epithelioma occurring on the arms of paraffin- and tar-workers;† further to those much-discussed cases, in which an unquestionable cancerous ulceration develops at the base and out of a chronic ulcer, due to a traumatic or to some specific cause, such as lupus. I have no desire to dispute the justice of attributing to all these ulcerative processes a malignant—cancerous—character; for the criterion of malignancy, namely the diminished resisting power of the tissues of the vicinity—in this instance the vascular connective tissue bordering on the epithelium—is here found in a marked degree. The reason I feel compelled, in spite of this, to separate them from the carcinomata proper, *i.e.* from the *cancerous tumours*, is that there is here not the slightest likelihood, to say nothing of necessity, that they should be referred to a congenital

* Cf. Billroth, 'Allg. chir. Pathol. Vorles.,' 50.

† Cf. Tillmanns, 'D. Zeitschr. f. Chir.,' xiii, p. 519.

cause. Should anyone, however, be disposed to draw an opposite inference, and say that the hypothesis of a congenital cause may be dispensed with for the remaining tumours also, I may refer him in the first place to the striking differences just noticed in the course of these cancer-like ulcers when contrasted with the true carcinomata; but before all I would wish to remind him that what is true of the epidermis need not therefore apply to all other tissues, not even to the remaining epithelia.

A process like that leading to superficial cancer of the skin can occur only where new cells are produced without interruption in the normal condition, and come into contact with a heterologous tissue—only, that is, in the *laminated epithelia.* For this there is in particular no analogue in the *glands.* In them, after growth is completed, cell-formation takes place only during secretion, and is consequently dependent on nervous influence; here it will doubtless be quite immaterial whether the physiological resistance of the interlobular connective tissue be much or little. *Hence there can be no cancer of a gland which is not at the same time a true tumour.* But it is precisely the glandular carcinomas that present the best examples of a *benign adenomatous* stage, often of long duration, followed by a cancerous one. In them, therefore, the course of the malignant tumours may be most satisfactorily demonstrated. Picture to yourselves an adenoma —small or large—a gland-like yet atypical nodule, whose cell-tubes or vesicles are more or less evidently connected with the normal gland-tubuli or acini, but enveloped in connective tissue. What will happen if now for any reason the resisting power of the connective tissue be destroyed, while the growing capacity of the adenoma is not only not reduced, but most energetic? The cells of the adenoma will no longer push the connective tissue aside; *they will penetrate into it.* In doing so they will of necessity very soon meet with a *lymph-space,* and in this way enter the lymphatics; and by the continued proliferation of the epithelial cells within the lymphatics in the manner already referred to, will be formed *branched epithelial processes,* separated from one another by, or embedded in, vascular connective tissue. In saying which I do not mean to imply that the growing epithelial cylinders

are confined in their progress to the interior of the lymph-vessels. The behaviour of the connective tissue into which the epithelial processes grow, and of its vessels, may vary greatly. At one time there is but a trifling reaction, at another all the signs of inflammatory hyperæmia and cell extravasation are observed !* But, however this may be, the typical *carcinoma* is now complete. How the epithelial cells are thereupon washed into the nearest lymphatic glands to eventually form the germs of new cancer-nodules has been already described. The *alveolar structure* seen in cancerous lymphatic glands is also chiefly owing to the circumstance that the masses of epithelium spread first of all through the lymph-sinuses of the cortical and medullary substance and not till afterwards grow out in a perfectly atypical way into the cortical nodules or medullary cords, or into the connective tissue surrounding the gland. The invasion and cancerous infiltration of the lymphatic glands commences as a rule in a particular direction. In carcinoma of the mamma, for example, the axillary glands are usually first affected. After a time, however, glands lying in another direction are wont to become involved in the process. Cancerous enlargement of the axillary glands is followed by a similar enlargement of the supra-clavicular. Meanwhile the primary tumour has been extending *in loco* on all sides. The tissues which have lost their capacity for resistance become involved one after another until (to adhere to our example) the skin is infiltrated, and the cancer appears on the surface—a result which is sometimes brought about by necrosis through the pressure of the tumour on the overlying skin, to which it is firmly adherent. It is essentially immaterial whether the local extension of the cancer occurs continuously, so as to give to the naked eye the appearance of a compact mass, or whether small, apparently isolated, or, as they are termed, disseminated nodules, form in the vicinity of the principal tumour and afterwards coalesce with it. For in many cases the separation of the daughter-nodules from the mother-tumour is apparent only, and an epithelial band of microscopic size may quite commonly be detected between them. Where, however, actual dissemination is present, it is the agency of

* Waldeyer, 'Virch. A.,' lv, p. 152.

the lymphatics that no doubt brings it about. When this point is arrived at, true metastases are not long in making their appearance. When the elements of a tumour commence to circulate with the blood, having entered it either from the lymphatic glands by means of the v. efferentia or directly by penetrating the blood-vessels, the formation of metastases becomes possible. Wherever the epithelial cells or cell-masses get arrested in the vascular system they form fresh centres of growth. These are at first confined to the interior of the vessels, and then, if the resisting power of the affected locality is destroyed, they break through the vessel wall, and grow into the surrounding tissues. Here they form secondary cancerous tumours, often of enormous size, with a structure the more markedly alveolar, the more the epithelial masses settle in the lymph-channels.

What has just been stated with regard to the course of cancer in glandular organs is strictly applicable not only to the true or—in the language of the clinician—*deep* cancers of the skin and mucous membrane, but *to the malignant tumours generally*. It is not possible for a tumour to become malignant except the physiological resistance of the surrounding tissues is extinguished. When, however, this has occurred, malignant characters will most certainly manifest themselves in those tumours *whose growing energy is greatest.* We know that this energy is directly related to the cell-richness of any class of tumours; and that, among the cellular tumours, those more especially are distinguished by its possession whose cell-type belongs to a *very early embryonic period.* It is for this reason that the sarcomas sometimes acquire such fearfully malignant properties. It is not, however, the sarcomatous structure that renders a tumour malignant; but when the conditions of malignancy are present in the organism, this structure enables the tumour to take advantage of those conditions to the greatest conceivable degree. All other varieties of tumours, rich in cells, and especially in cells of an embryonic character, may, under such conditions, become malignant and generalised. We see this both in *lymphomas* and *enchondromas;* in the latter of which the danger of generalisation is more pronounced the greater their richness in cells and the softer and more

mucous their consistence. In other words their malignancy is marked in proportion as they approach the type of the earliest embryonic cartilage. We learn this also from the *myxomas;* for though these are true embryonic tumours, only the most cellular forms give rise to metastases. The same thing applies to the *gliomas,* of which the retinal form alone is malignant, while the glioma of the brain is rather the equivalent in structure of the developed central nervous system.* In the last place, the smooth and striped myomas, when they give rise to metastases, always display marked embryonic characters. Conversely it is easy to explain in this way why osteomas, lipomas, fibromas, angiomas, neuromas, goitres, and cystomas do not produce metastases, even though the simultaneous presence of a cancer is proof that the conditions of malignancy exist in the body. True, with some of these tumours generalisation is not absolutely impossible; and the occasional occurrence of metastatic lipomas, fibromas, and even goitres, I regard as a most desirable piece of evidence for the truth of our theory of malignancy.

But whatever be the histological structure of a tumour, the manner and mode of development of its malignancy is in every case the same. It is immaterial whether it was previously sharply circumscribed or diffuse; for with the commencement of malignancy, *i.e.* of the ingrowth into the tissues of the vicinity, *its circumscribed character is obviously at an end.* It is no less immaterial whether the tumour has or has not attained in its benign stage considerable dimensions. A sarcoma of bone or a lymphoma may be of vast size before it involves the neighbouring tissues or produces metastases; while a melanotic sarcoma of the choroid, hardly so large as a hazel nut, can give rise to metastases so bulky and numerous as scarcely to have a parallel in the worst cases of carcinoma. For the criterion of malignancy consists, on our view, neither in the size, nor in the structure, nor again in the rate of growth of a tumour, but *only and solely in the behaviour of the other tissues of the body.* A lymphoma of the neck may perhaps become as large as, or larger than, a man's fist in a comparatively short time, and prove burdensome enough to the subject of it. Still it is, and remains, a

* Klebs, 'Prag. Vierteljahrsschr,' Bd. cxxxiii.

benign tumour so long as it does not exceed the limits of the gland and may be easily raised out of the tissues surrounding it. When, on the other hand, the lymphoma has broken through the capsule of the gland, and grown into the adjacent connective tissue, it constitutes an eminently malignant tumour, spreading itself rapidly through the locality and giving rise to metastases in remote lymphatic glands, and in the lungs, liver, spleen, kidneys, bones, &c.* There is, in my opinion, no real reason for supposing that the cases of the latter category are examples of quite another variety of tumour, which is therefore contrasted with the "lymphoma" under the special name of "lymphosarcoma." The *myelogenic sarcoma* does not receive this name from the moment of its breaking through the periosteum and commencing to grow into the surrounding connective tissue or muscles; and no one thinks of terming the same tumour a *myeloma*, while its growth is merely expansive, and it simply presses aside or erodes the compact substance of the bone. A terminology such as is customary in cases of epithelial tumour has never been in vogue for the connective-tissue group. An epithelial tumour, on becoming malignant, at once receives the name "cancer," "carcinoma," with its various sub-varieties; and we consequently speak of *cancerous degeneration* of an adenoma, an epithelioma, a goitre, or a cystoma. No such notion is connected with the expression "sarcoma;" by it we understand a form of tumour, which may like most others be innocent or malignant: a "benign cancer" is an absurdity; a "benign sarcoma" is fortunately not uncommon. If, moreover, I be correct in the supposition expressed on another occasion (vol. ii, p. 743), namely, that a number of the tumours nowadays recorded under the name "lymphosarcoma" are in reality infective in their origin, and consequently to be classed with the infective tumours, it will I think be very advisable to reserve this term for the infective growths, while of the true tumours of lymphatic structure the benign lymphoma is simply contrasted with the malignant one.

It is clear from the foregoing that the various cases of

* Lücke, l. c., p. 192; Virchow, 'Geschwülste,' ii, Vorles. 21; cf. Langhans, 'Virch. A.,' liv, p. 509.

malignant and generalised tumour have many features in common. In fact, most of the differences and peculiarities in the course of the several forms of malignant growth can already be traced to the anatomical disposition of the locality in which they originate and to the histological structure of the primary tumour. That sarcomas, owing to their richness in cells, and the markedly embryonic character of them, are endowed with an unusual degree of growing energy, I have stated more than once. It is this capacity, in which on the average they considerably surpass the cancers, that explains why sarcomas, when once they have become malignant, are *much more ruthless in their local ravages* than are the carcinomas, as well as far less disposed to confine themselves to the lymphatics. That they may be so confined is obvious, and besides is most clearly illustrated by many *exquisite alveolar sarcomas.* The not uncommon sarcomatous infiltrations of the nearest lymphatic glands shows that the lymph-stream may form a means of dissemination. Yet it is a fact, on which Virchow and others have rightly laid stress, that the sarcomata either pass over the lymphatic glands, or that metastases more readily occur in glands further removed than those which receive their lymph from the region of the primary tumour. The cause of this apparently paradoxical behaviour is no doubt, as Lücke* believes, the comparatively small size of the cells of a sarcoma. The small round and spindle-cells, of which the metastases in question are mainly composed, easily pass the same lymphatic glands in which the considerably larger epithelial cells are arrested. An invasion of the blood by sarcoma-cells is consequently all the more certain, and will be brought about partly by the circuitous path of the lymphatics, and partly by direct penetration into the interior of blood-vessels, a task for which many of them are specially qualified by their power of spontaneous locomotion. This property of contractility has, at any rate, again and again been detected by good observers in the cells of sarcomatous tumours; so that one is justified in asking whether the *local dissemination* of this form is not often effected by *wandering* sarcoma-cells.

Generalisation by means of the blood-vessels is far from

* Lücke, 'Volkmann'sche Vort.,' No. 97.

being a peculiarity of the sarcomas. The extreme frequency with which abominal carcinoma is followed by metastases in the *liver,* and only in this organ, tells in the clearest way for its distribution *by means of the circulation.* The metastases are true cancerous emboli; *i. e.* they were originally cancerous thrombi, which, seized upon by the blood-stream, are now transported through the blood-vessels as far as the narrowing of their calibre admits. In a precisely similar manner are formed most of the secondary pulmonary nodules, originating in primary malignant tumours of other regions; and it is very characteristic that *giant-cell sarcoma of bone,* if it becomes generalised, almost invariably gives rise to metastases in the lungs. When, however, the tumour-cells entering the blood-stream are so small as to circulate without obstruction through the entire vascular system, their arrest is as little controlled by the laws of embolism as is the distribution of cinnabar or of minute colonies of bacteria. Where they are ultimately arrested depends, if you will, on accident; yet the *velocity of the flow* in a vascular area is certainly a very essential factor. The less the velocity, the more favorable are the conditions for a temporary halt and for commencing proliferation. In this fact you may see one of the essential reasons for the preference shown by metastases of all kinds first of all for the *liver* and next for the *bone-marrow,* and that too quite irrespective of the situation of the primary growth. But the arrest and commencing proliferation in the interior of a blood-vessel does not, as already determined, involve the development of a secondary nodule. For this a falling off in the physiological resistance of the tissues of a part is necessary; and it will therefore be expedient to consider always whether any influence is exerted by this factor on the localisation of the metastases. The seed—the cells that have entered the blood—may be distributed everywhere, but arrive at development only in particular organs or tissues.

Here too it is no part of my task to place on a broader basis the principles just expounded by citing all possible varieties of cases. Nor, so far as I can judge, do any serious difficulties present themselves. The absolute *immunity of cartilage* from metastases, already dwelt on, is explained in the simplest way by the *absence of lymph- and blood-vessels;*

and this immunity therefore affords a welcome proof for the cellular nature of the metastases, and against infection by the juices; since cartilage is by no means inaccessible to the latter. Further it is quite intelligible that metastases from genuine abdominal myomas* should be seen nowhere except in the *liver* and in the *diaphragm*, into the latter of which the muscle-germs are conveyed by the peritoneal lymph-stream, just as happens with bacteria, milk-globules, &c. An explanation of those much-discussed cases of *general miliary carcinosis* by our theory of transport is the less hazardous as in them we have invariably to deal with small-celled cancers, and as the presence of unmistakable cancer-cells in the blood has repeatedly been determined by trustworthy writers.† But none of these individual cases can teach us anything new, or present our theory in a new light. Hence it appears more advantageous to turn our attention to a most important dogmatic point; and to ask *how are the malignant tumours infective*, or, in other words, whether their infectiveness differs from that of the infective inflammations and infective tumours, and if so in what respects. As a matter of fact, the courses run by the malignant tumours and by the two processes last named present at first sight a very striking resemblance. A person is attacked by an infective inflammation of the face; the superior cervical glands swell first, and then the inferior and deeper ones; and, if things take a mischievous turn, no long time elapses before pulmonary and hepatic abscesses, and eventually suppuration of the joints, with foci in the kidneys, spleen, and muscles, make their appearance, or the serous membranes become involved in the process. Is not this a faithful history of cancer of the face, except that in the latter the metastases are cancerous, in the former inflammatory? Is it not also the history of syphilis, of glanders, and often of tuberculosis? On the primary induration of the penis there follows first the infiltration of the inguinal glands; various eruptions soon appear on the skin; and then the palate, the lips, and finally all possible internal or external organs may become affected. The dissemination of glanders from the nasal mucous mem-

* Eberth, 'Virch. A.,' lv, p. 518; Brodowsky, ibid., lxvii, p. 227.

† Demme, 'Schweiz. Monatsschr. f. pr. Med.,' 1858, No. 6.

brane through the lymphatics and glands of the neck, and thence to the lungs, muscles, &c.; the spreading of tuberculosis from the lungs to the bronchial glands, the pleuræ, and then to the intestines, liver, spleen, and membranes of the brain—is it possible to imagine more typical forms of generalisation? More than this; a general miliary carcinosis may so closely resemble general miliary tuberculosis as that one may be mistaken for the other. Even the urogenital tuberculosis, apparently so characteristic, is sometimes perfectly represented by a urogenital carcinosis and urogenital sarcomatosis.* Like the tubercular affection, the latter progress from the testicle to the spermatic cord, the bladder and prostate, the ureters, pelves of the kidneys, and kidneys themselves. Truly, if the former be an infective process, can any doubt whatever be entertained as to the infective nature of the malignant tumours?

But a moment's reflection will show that the mode of dissemination and the localisation of the process afford no ground for a conclusion as to its nature. When cinnabar is introduced beneath the skin, you find the characteristic granules in the nearest lymphatic glands; on injecting it into a vein, it immediately fills the pulmonary capillaries; but who would therefore credit cinnabar with infective qualities? No, the often described dissemination of all these processes proves absolutely nothing but *the participation in it of the blood- and lymph-streams;* it throws not the slightest light on the nature of the agent to which the affections in question are due. In previous lectures I have given in detail the evidence on which we base our assumption that the infective inflammations as well as the infective tumours are produced by a virus, *i. e. by a substance foreign to the organism as such, endowed with an almost unlimited capacity for reproduction, and consequently an organised one.* As regards the virus of the infective inflammations, its *bacterial* character has repeatedly been demonstrated; and that a similar virus is present in the infective tumours is at least probable, though we have not as yet succeeded in discovering the particular organism present in very many of these diseases. But how is it as regards the assumed virus of the malignant tumours,

* Prep. No. 115 in the Museum at Breslau, 1876.

or rather the different kinds of virus—for one must of necessity assume the existence of a separate virus for carcinomas, sarcomas, enchondromas, myxomas, myomas, gliomas, &c.? Now we need not discuss possibilities, *inasmuch as no such virus exists.* This is proved *by the impossibility of communicating malignant tumours to other individuals* in a manner similar to that which so certainly, one might almost say, invariably succeeds both in infective inflammations, and in syphilis, glanders, and the remaining infective tumours. This single fact suffices to exclude all apparent analogy with the true infective diseases. But we are also in the agreeable position of being able to point to the causes determining the similar course of the processes, on the one hand, and their essentially dissimilar nature, on the other. The dissemination of the infective inflammations and tumours takes place through the agency of the lymph- and blood-streams, just as does that of the malignant growths; but in the former diseases the *virus* is disseminated, in the latter *fragments from the malignant tumours themselves.* In the former, the virus is carried by the lymph-stream to the lymphatic glands and serous membranes, or by the blood-stream to the liver, spleen, kidneys, &c.; or it creeps along a mucous membrane, and excites an inflammation, or gives rise to a gumma, a farcy nodule, or a tubercle wherever it arrives. In the latter it is the tumour-cells that are carried off, or that extend over and infiltrate a large area by continuously growing. In the latter, tissue-cells from the body form the seed; in the former, so little does dissemination depend upon cells that caseous detritus is just as active as the freshest clear grey tubercle, and that serum from a focus of infective suppuration gives rise to the most pronounced inflammation. The malignant tumours have no definite incubation period, such as is so characteristic of syphilis, glanders, the infective inflammations, and tuberculosis. And while the malignant growths have another point of similarity with the infective tumours, namely that removal of the primary focus is of no avail when once a dissemination of the virus or of the tumour-cells has taken place through the body, on the other hand we know nothing of a *spontaneous healing* of malignant tumours, such as happily occurs often enough in syphilis and

even in tuberculosis. Finally, as regards inheritance, the same distinctions are found. In the tumours, the redundant germinal material is inherited, just as is a sixth finger or a thirteenth rib; and possibly too the feeble resisting power of the tissues is transmitted to the offspring. As for hereditary syphilis, I referred on a former occasion (vol. i, p. 381) to the probability that the virus contaminates the semen or ovule, and is communicated to the future embryo during procreation.

Let us consider in conclusion the *significance* of tumours for the organism. You will remember my having laid stress on the fact *that they are* eo ipso *incapable of doing work, of performing any function.* A tumour, consequently, can never be of service to its possessor, but rather the more injurious. In this connection, I cannot of course enter into a detailed explanation of the innumerable *local detrimental effects* which may attend the presence of a tumour. All such considerations will be advantageously reserved for the pathology of the individual organs; here we shall confine ourselves to such points as apply to all tumours irrespective of locality. By far the most important element in, the fundamental significance of, a tumour consists in the fact that by it, or rather by its development, *a quantity of highly organised material is withdrawn from the organism.* So far, the ancient view, according to which every tumour is a kind of *parasite,* is far from incorrect. For all tumours grow at the expense of the rest of the organism, which assuredly cannot apply the material consumed in building up the tumour to its own aims and uses. But whatever the use made of the material, it would at any rate be more beneficial to the body than when thus appropriated. The tumour is absolutely of no service; and it is even very doubtful whether, for example, a lipoma has the same value for its possessor as has an accumulation of fat on the abdomen. For the latter may be burdensome enough, but should things go badly with its subject, it can contribute towards his expenditure; while it is by no means clear that a lipoma will enable him to hold out better under lasting privation. The extent to which the body will be prejudiced by a tumour depends, it is plain, for one thing on

its *size*, but above all on *the rapidity of its growth.* For if a tumour grows very slowly it may ultimately acquire very respectable dimensions without at any time interfering with the bodily functions more than would *e.g.* a chronic nasal catarrh. Not so, of course, when its growth is rapid. This it is, in particular, that greatly contributes to the dangerous character of sarcomas; it is this that mainly causes the malignant tumours to be so dreaded. Picture to yourselves the metastases of a carcinoma of the stomach or of a malignant lymphoma as all united to form one compact mass, and you will not uncommonly find that in the course of a few months tumour-tissue weighing ten to twelve kilos or more is produced—and this, as a rule, in a body whose physiological constitution just enables it to maintain its equilibrium; or, in young individuals, in excess of the physiological measure of growth.

To all this must be added another factor, at least in the great majority of tumours. If we neglect those growths which project freely above the surface of the body in polypus fashion, or grow into a cavity where space is secured by distension of the walls, *it must inevitably happen that wherever a mass of tumour develops normal tissue perishes.* And here it is quite immaterial whether a tumour is benign or malignant; room must at all costs be procured, and this object is in both instances realized by *pressure-atrophy.* At most in the manner of this atrophy there are certain differences; thus, *e. g.* an innocent tumour causes muscular atrophy by compression from without, while the same result is achieved by a malignant one through the growth of its cells between the muscle-fibres and even into the sarcolemma; but in both instances the effect is due to *pressure-atrophy.* Just as the mechanical results to the circulation are the same whether a tumour compresses a vein from without or, having penetrated it, acts as a thrombus by obstructing its lumen, so also in the present case. The cancer-cells neither consume the tissue-elements nor cause their solution, but the latter yield before the pressure exerted in growth and gradually disappear—an effect which is no doubt actively promoted by the anæmia consequent upon compression. Here we find a second prejudicial factor; not only are absolutely worthless masses of

tissue produced at the cost of the organism, but *there is a destruction of parts which are of importance to the body,* inasmuch as they form portions of its physiological treasure. It is unnecessary to enlarge upon the fact that malignant tumours must also in this respect be much more detrimental than benign ones, in that by reason of their generalisation they may be destructive to several different organs at the same time.

We know far too little of the metabolism of the tumours to say positively how much good and useful material is withdrawn from the body for their *nourishment.* As repeatedly stated, there is no kind of waste as the result of work in tumours. But this does not of course exclude the possibility that in them, more especially when rich in cells, a more or less active waste and repair may constantly be taking place. At any rate, the facts already referred to with respect to the occurrence of *fatty changes, calcification,* and *of all kinds of nutritive derangements* in tumours hardly admit of any other explanation. Nor, if we disregard the withdrawal of material, are we sufficiently informed as to whether any prejudicial effect is exerted on the organism by the metabolic changes occurring in tumours. That the absorption of tumour-tissue which has undergone fatty or simple atrophy should be injurious to the body can scarcely be believed; still less can it be supposed that evil consequences attend the calcification, or the colloid or amyloid degeneration, of portions of a tumour. Even if the direct penetration of malignant tumours into the lymph- and blood-vessels be taken into account, so great will then be the danger of metastases that the alteration in the blood will be of comparatively little moment. For though it is true—and easily understood moreover—that various epithelial or spindle-cells, and in melanotic tumours pigmented ones, will in such circumstances circulate in the blood, yet they are usually far too few in number to produce even the slightest circulatory disturbance. Such an inundation of the blood with tumour-cells as Lücke* observed in a case of lymphosarcoma of the axillary glands with penetration of the subclavian vein is at any rate a very exceptional occurrence.

* Lücke, 'Virch. A.,' xxxv, p. 524.

As regards one group of nutritive disturbances in tumours, however, we know but too surely that it may be attended by considerable danger to the organism as a whole. I refer to *necrosis* and the decompositions setting in in its train. A simple necrosis, such as not uncommonly occurs in the interior of a large tumour, owing to occlusion of a vessel, &c., can scarcely, it is true, be a serious event. But when any kind of abnormal decomposition takes place in the necrotic tissue, a door is opened for most pernicious consequences. In the tumour itself a purulent inflammation is set up; pyrexia—which nowise belongs to the clinical picture of tumours, whether malignant or benign—is developed; and if particles be now carried off from the tumour, the result is not simply the formation of metastases *but the setting up of inflammation also.* Such are the cases, so frequently misunderstood, of carcinoma of the lymphatic glands complicated by adenitis, and of carcinomatous pleuritis and peritonitis. When, as may happen in the worst cases, the tumour becomes foul and putrid, general *septicæmia* and *ichorrhæmia* are wont to set in.

There are, you perceive, factors in plenty, by which a tumour may prove prejudicial and dangerous to the organism. In fact it is by no means necessary to refer to the *suppuration* and *hæmorrhage* which are inseparable from the ulceration of a tumour in order to explain how it comes to pass that individuals grow thin and feeble, become *anæmic* and *hydræmic,* under the influence of the neoplasm. I have also, I think, sufficiently dwelt on the causes which render the malignant tumours especially calculated to undermine the health and constitution. They are wont rapidly to reach a considerable size; a large number of organs and tissues are simultaneously affected by them; and they are peculiarly predisposed to necrosis and ulceration, if for no other reason because they become adherent to the coverings of the body. Still—you will carefully note this—*cachexia* does not inevitably ensue on malignant growths. A malignant tumour which does not ulcerate, does not grow very large, and gives rise only to small metastases need not in the least interfere with the general well-being. Indeed, if it be hidden in the deeper parts, as is, *e. g.* a carcinoma in the commencement of the

pyloric region with metastases in the liver, the entire carcinosis may be so latent in its course as only to be discovered by accident at the *post-mortem.* On the other hand, I need only remind you of the course run by many submucous uterine myomas, attended as they are by profuse menorrhagia, in order to show that tumours thoroughly innocent *per se* may prove highly injurious to the organism. These are facts that should be taken to heart; and just as I formerly protested against the notion that malignancy is connected with certain peculiarities of histological structure, so now I desire expressly to point out that malignancy in the course of a tumour by no means invariably, though often, involves what I may venture to call *clinical malignancy.* If this be so the much-discussed conception of a *cancerous cachexia* or *dyscrasia* falls to the ground—meaning thereby a specific general affection of the body of which the cancerous tumour is but a localisation. In explanation of a number of cases of malignant tumours, we too found it necessary to have recourse to the hypothesis of a "feebleness" of the tissues of unknown nature; but I need hardly say that *this "feebleness" has nothing whatever in common with cachexia.* The nutrition of a body may be excellent, and yet the resisting capacity of its tissues minimal. The most pernicious and malignant retinal gliomas are met with precisely in robust children; and I had lately the opportunity of examining *post mortem* an extremely well-developed and well-nourished body—that of a servant-maid, aged twenty-six, who died in childbed—and discovered therein a small ulcerated carcinoma of the stomach with many metastases in the liver, while both ovaries were transformed into cancerous tumours, each larger than a child's head. Such an occurrence is, it is true, only possible when the digestive and hæmapoietic apparatus of the body perform their functions regularly, and when no fever or other malady is present to lower the bodily strength. But when these conditions are satisfied, such a course as has been described is by no means an unheard-of rarity. On the contrary, many a physician has been filled with astonishment at the capabilities of the human organism, which enable it to assimilate such enormous quantities of material as are necessary at once to maintain its own nutritive condition intact,

and to produce the tumours. But inasmuch as the extreme capacity of the human body must always be sooner exhausted than will be the growing capacity of a tumour, especially if malignant, it is under all circumstances advisable to remove a tumour so early and completely that no vestige of it may remain at its seat of origin, and that its dissemination through the body may have been anticipated.*

* On the subject of Tumours consult further Virchow, 'Die krankhaften Geschwülste,' i—iii, Berlin, 1863 to 1867; Lücke, in Pitha-Billroth's 'Handb.,' ii, 1; Billroth, 'Allgem. chir. Path. und Therapie,' Cap. 20; cf. the handbooks of Gen. Pathol. and Path. Anatomy of Wagner, Rokitanski, Förster, R. Mayer, Birch-Hirschfeld, Perls, Ziegler, &c.

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Lectures on general pathology